Rochester
2018 Interpretive Handbook

Sorted By Test Name

Current as of October 11, 2018 2:20 pm CDT
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Definition of Specimen "Minimum Volume"

Defines the amount of specimen required to perform an assay once, including instrument and container dead space. Submitting the minimum specimen volume makes it impossible to repeat the test or perform confirmatory or perform reflex testing. In some situations, a minimum specimen volume may result in a QNS (quantity not sufficient) result, requiring a second specimen to be collected.
POLICY STATEMENTS

Animal Specimens
We do not accept animal specimens for laboratory testing.

Billing

Client—Each month you will receive an itemized invoice/ statement which will indicate the date of service, patient name, CPT code, test name, and test charge. Payment terms are net 30 days. When making payment, please include our invoice number on your check to ensure proper credit to your account.

Patient—Mayo Medical Laboratories does not routinely bill patient’s insurance; however, if you have made advanced arrangements to have Mayo Medical Laboratories bill your patient’s insurance, please include the following required billing information: responsible party, patient’s name, current address, zip code, phone number, Social Security number, and diagnosis code. Providing this information will avoid additional correspondence to your office at some later date. Please advise your patients that they will receive a bill for laboratory services from Mayo Medical Laboratories for any personal responsibility after insurance payment. VISA® and MasterCard® are acceptable forms of payment.

Billing—CPT Coding
It is your responsibility to determine correct CPT codes to use for billing. While this catalog lists CPT codes in an effort to provide some guidance, CPT codes listed only reflect our interpretation of CPT coding requirements and are not necessarily correct. Particularly, in the case of a test involving several component tests, this catalog attempts to provide a comprehensive list of CPT codes for all of the possible components of the test. Only a subset of component tests may be performed on your specimen. You should verify accuracy of codes listed. Where multiple codes are listed, you should select codes for tests actually performed on your specimen. MAYO MEDICAL LABORATORIES ASSUMES NO RESPONSIBILITY FOR BILLING ERRORS DUE TO RELIANCE ON CPT CODES LISTED IN THIS CATALOG. For further reference, please consult the CPT Coding Manual published by the American Medical Association. If you have any questions regarding use of a code, please contact your local Medicare carrier.

Business Continuity and Contingency Planning
In the event of a local, regional, or national disaster, Mayo Clinic and Mayo Medical Laboratories’ performing sites have comprehensive contingency plans in place in each location to ensure that the impact on laboratory practice is minimized. With test standardization between our performing sites and medical practice locations throughout the country, we have worked to ensure that patient care will not be compromised.

Cancellation of Tests
Cancellations received prior to test setup will be honored at no charge. Requests received following test setup cannot be honored. A report will be issued automatically and charged appropriately.

Chain-of-Custody
Chain-of-custody, a record of disposition of a specimen to document who collected it, who handled it, and who performed the analysis, is necessary when results are to be used in a court of law. Mayo Medical Laboratories has developed packaging and shipping materials that satisfy legal requirements for chain-of-custody. This service is only offered for drug testing.
Compliance Policies
Mayo Medical Laboratories is committed to compliance with applicable laws and regulations such as the Clinical Laboratory Improvement Amendments (CLIA). Regulatory agencies that oversee our compliance include, but are not limited to, the Centers for Medicare and Medicaid Services (CMS), the Food and Drug Administration (FDA), and the Department of Transportation (DOT). Mayo Medical Laboratories develops, implements, and maintains policies, processes, and procedures throughout our organization which are designed to meet relevant requirements. We expect clients utilizing our services will ensure their compliance with patient confidentiality, diagnosis coding, anti-kick back statutes, professional courtesy, CPT-4 coding, CLIA proficiency testing, and other similar regulatory requirements. Also see “Accreditation and Licensure,” “HIPAA Compliance,” and “Reportable Disease.”

Confidentiality of Results
Mayo Medical Laboratories is committed to maintaining confidentiality of patient information. To ensure Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the College of American Pathologists (CAP) compliance for appropriate release of patient results, Mayo Medical Laboratories has adopted the following policies:

Phone Inquiry Policy—One of the following unique identifiers will be required:

- Mayo Medical Laboratories’ accession ID number for specimen; or
- Client account number from Mayo Medical Laboratories along with patient name; or
- Client accession ID number interfaced to Mayo Medical Laboratories; or
- Identification by individual that he or she is, in fact, “referring physician” identified on requisition form by Mayo Medical Laboratories’ client

Under federal regulations, we are only authorized to release results to ordering physicians or health care providers responsible for the individual patient’s care. Third parties requesting results including requests directly from the patient are directed to the ordering facility. We appreciate your assistance in helping Mayo Medical Laboratories preserve patient confidentiality. Provision of appropriate identifiers will greatly assist prompt and accurate response to inquiries and reporting.

Critical Values
The “Critical Values Policy” of the Department of Laboratory Medicine and Pathology (DLMP), Mayo Clinic, Rochester, Minnesota is described below. These values apply to Mayo Clinic patients as well as the extramural practice administered through affiliate Mayo Medical Laboratories. Clients should provide contact information to Mayo Laboratory Inquiry to facilitate call-backs. To facilitate this process, a customized form is available at mayomedicallaboratories.com

Definition of Critical Value—A critical value is defined by Mayo Clinic physicians as a value that represents a pathophysiological state at such variance with normal (expected values) as to be life-threatening unless something is done promptly and for which some corrective action could be taken.

Abnormals are Not Considered Critical Values—Most laboratory tests have established reference ranges, which represent results that are typically seen in a group of healthy individuals. While results outside these reference ranges may be considered abnormal, “abnormal” results and “critical values” are not synonymous. Analytes on the DLMP Critical Values List represent a subgroup of tests that meet the above definition.

Action Taken when a Result is Obtained that Exceeds the Limit Defined by the DLMP Critical Values List—In addition to the normal results reporting (eg, fax, interface), Mayo Medical Laboratories’ staff telephone the ordering physician or the client-provided contact number within 60 minutes following laboratory release of the critical test result(s). In the event that contact is not made within the 60-minute period, we continue to telephone until the designated party is reached and the result is conveyed in compliance and adherence to the CAP.
**Semi-Urgent Results**—Semi-Urgent Results are defined by Mayo Clinic as those infectious disease-related results that are needed promptly to avoid potentially serious health consequences for the patient (or in the case of contagious diseases, potentially serious health consequences to other persons exposed to the patient) if not acknowledged and/or treated by the physician. While not included on the Critical Values List, this information is deemed important to patient care in compliance and adherence to the CAP.

To complement Mayo Medical Laboratories’ normal reporting mechanisms (eg, fax, interface), Mayo Medical Laboratories’ staff will telephone results identified as significant microbiology findings to the ordering facility within 2 hours following laboratory release of the result(s). In the event that contact is not made within the 2-hour period, we will continue to telephone until the responsible party is reached and the result is conveyed. In addition, in most instances, you will see the comment **SIGNIFICANT RESULT** appear on the final report.

For information regarding the Mayo Clinic Critical Value List, contact Mayo Medical Laboratories at 800-533-1710 or 507-266-5700 or visit mayomedicallaboratories.com.

**Disclosures of Results**
Under federal regulations, we are only authorized to release results to ordering physicians or other health care providers responsible for the individual patient’s care. Third parties requesting results, including requests directly from the patient, are directed to the ordering facility.

**Extracted Specimens**
Mayo Medical Laboratories will accept extracted nucleic acid for clinical testing, provided it is an acceptable specimen source for the ordered test, if the isolation was performed in a CLIA-certified laboratory or a laboratory meeting equivalent requirements as determined by the CAP and/or the CMS.

**Fee Changes**
Fees are subject to change without notification and complete pricing per accession number is available once accession number is final. Specific client fees are available by calling Mayo Laboratory Inquiry at 800-533-1710 or 507-266-5700 or by visiting mayomedicallaboratories.com.

**Framework for Quality**
“Framework for Quality” is the foundation for the development and implementation of the quality program for Mayo Medical Laboratories. Our framework builds upon the concepts of quality control and quality assurance providing an opportunity to deliver consistent, high-quality and cost-effective service to our clients. In addition, our quality program enhances our ability to meet and exceed the requirements of regulatory/accreditation agencies and provide quality service to our customers.

A core principle at Mayo Medical Laboratories is the continuous improvement of all processes and services that support the care of patients. Our continuous improvement process focuses on meeting the needs of you, our client, to help you serve your patients.

“Framework for Quality” is composed of 12 “Quality System Essentials.” The policies, processes, and procedures associated with the “Quality System Essentials” can be applied to all operations in the path of workflow (eg, pre-analytical, analytical, and post-analytical). Performance is measured through constant monitoring of activities in the path of workflow and comparing performance through benchmarking internal and external quality indicators and proficiency testing.

Data generated by quality indicators drives process improvement initiatives to seek resolutions to system-wide problems. Mayo Medical Laboratories utilizes “Failure Modes and Effects Analysis (FMEA),” “Plan Do Study Act (PDSA),” “LEAN,” “Root Cause Analysis,” and “Six Sigma” quality improvement tools to determine appropriate remedial, corrective, and preventive actions.
Quality Indicators—Mayo Medical Laboratories produces hundreds of Key Performance Indicators for our business and operational areas, and we review them regularly to ensure that we continue to maintain our high standards. A sampling of these metrics includes:

- Pre-analytic performance indicators
  - Lost specimens*
  - On-time delivery
  - Special handling calls
  - Specimen acceptability*
  - Specimen identification*
  - Incoming defects*
- Analytic performance indicators
  - Proficiency testing
  - Test reliability
  - Turnaround (analytic) times
  - Quantity-not-sufficient (QNS) specimens*
- Post-analytic performance indicators
  - Revised reports*
  - Critical value reports*
- Operational performance indicators
  - Incoming call resolution*
  - Incoming call abandon rate
  - Call completion rate
  - Call in-queue monitoring
  - Customer complaints
  - Customer satisfaction surveys

The system provides a planned, systematic program for defining, implementing, monitoring, and evaluating our services.

*Measured using Six Sigma defects per million (dpm) method.

HIPAA Compliance
Mayo Medical Laboratories is fully committed to compliance with all privacy, security, and electronic transaction code requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). All services provided by Mayo Medical Laboratories that involve joint efforts will be done in a manner which enables our clients to be HIPAA and the College of American Pathologists (CAP) compliant.

Infectious Material
The Centers for Disease Control (CDC) in its regulations of July 21, 1980, has listed organisms/diseases for which special packaging and labeling must be applied. Required special containers and packaging instructions can be obtained from us by using the “Request for Supplies” form or by ordering from the online Supply Catalog at mayomedicallaboratories.com/customer-service/supplies/index.php.

Shipping regulations require that infectious substances affecting humans be shipped in a special manner. See “Infectious Material.” A copy of the regulations can be requested from the International Air Transport Association (IATA); they may be contacted by phone at 514-390-6770 or faxed at 514-874-2660.

Informed Consent Certification
Submission of an order for any tests contained in this catalog constitutes certification to Mayo Medical Laboratories by ordering physician that: (1) ordering physician has obtained “Informed Consent” of subject patient as required by any applicable state or federal laws with respect to each test ordered; and (2) ordering physician has obtained from subject patient authorization permitting Mayo Medical Laboratories to report results of each test ordered directly to ordering physician.
On occasion, we forward a specimen to an outside reference laboratory. The laws of the state where the reference laboratory is located may require written informed consent for certain tests. Mayo Medical Laboratories will request that ordering physician pursue and provide such consent. Test results may be delayed or denied if consent is not provided.

**Non-Biologic Specimens**
Due to the inherent exposure risk of non-biologic specimens, their containers, and the implied relationship to criminal, forensic, and medico-legal cases, Mayo Medical Laboratories does not accept nor refer non-biologic specimen types. Example specimens include: unknown solids and liquids in the forms of pills, powder, intravenous fluids, or syringe contents.

**Patient Safety Goals**
One of The Joint Commission National Patient Safety goals for the Laboratory Services Program is to improve the accuracy of patient identification by using at least 2 patient identifiers when providing care, treatment, or services.

Mayo Medical Laboratories uses multiple patient identifiers to verify the correct patient is matched with the correct specimen and the correct order for the testing services. As a specimen is received at Mayo Medical Laboratories, the client number, patient name, and patient age date of birth are verified by comparing the labels on the specimen tube or container with the electronic order and any paperwork (batch sheet or form) which may accompany the specimen to be tested. When discrepancies are identified, the Mayo Laboratory call center will call the client to verify discrepant information to assure Mayo Medical Laboratories is performing the correct testing for the correct patient. When insufficient or inconsistent identification is submitted, Mayo Medical Laboratories will recommend that a new specimen be obtained, if feasible.

In addition, Anatomic Pathology consultation services require the Client Pathology Report. The pathology report is used to match the patient name, patient age and/or date of birth, and pathology case number. Since tissue blocks and slides have insufficient space to print the patient name on the block, the pathology report provides Mayo Medical Laboratories another mechanism to confirm the patient identification with the client order and labels on tissue blocks and slides.

**Parallel Testing**
Parallel testing may be appropriate in some cases to re-establish patient baseline results when converting to a new methodology at Mayo Medical Laboratories. Contact your Regional Manager at 800-533-1710 or 507-266-5700 for further information.

**Proficiency Testing**
We are a College of American Pathologists (CAP)-accredited, CLIA-licensed facility that voluntarily participates in many diverse external and internal proficiency testing programs. It is Mayo Medical Laboratories’ expectation that clients utilizing our services will adhere to CLIA requirements for proficiency testing (42 CFR 493.801), including a prohibition on discussion about samples or results and sharing of proficiency testing materials with Mayo Medical Laboratories during the active survey period.

Mayo Medical Laboratories’ proficiency testing includes participation in CMS-approved programs. Mayo Medical Laboratories also performs alternative assessment using independent state, national, and international programs when proficiency testing is not available. Mayo Medical Laboratories also conducts comparability studies to ensure the accuracy and reliability of patient testing, when necessary. We comply with the regulations set forth in Clinical Laboratory Improvement Amendments (CLIA-88), the Occupational Safety and Health Administration (OSHA), or the Centers for Medicare & Medicaid Services (CMS).

It is Mayo Medical Laboratories’ expectation that clients utilizing our services will adhere to CLIA requirements for proficiency testing including a prohibition on discussion about samples or results and sharing
of proficiency testing materials with Mayo Medical Laboratories during the active survey period. Referring of specimens is acceptable for comparison purposes when an approved proficiency-testing program is not available for a given analyte.

Radioactive Specimens
Specimens from patients receiving radioactive tracers or material should be labeled as such. All incoming shipment arriving at Mayo Medical Laboratories are routed through a detection process in receiving to determine if the samples have any levels of radioactivity. If radioactive levels are detected, the samples are handled via an internal process that assures we do not impact patient care and the safety of our respective staff. This radioactivity may invalidate the results of radioimmunoassays (RIA).

Record Retention
Mayo Medical Laboratories retains all test requisitions and patient test results at a minimum for the retention period required to comply with and adhere to the CAP. A copy of the original report can be reconstructed including reference ranges, interpretive comments, flags, and footnotes with the source system as the Department of Laboratory Medicine’s laboratory information system.

Referral of Tests to Another Laboratory
Mayo Medical Laboratories forwards tests to other laboratories as a service to its clients. This service should in no way represent an endorsement of such test or referral laboratory or warrant any specific performance for such test. Mayo Medical Laboratories will invoice for all testing referred to another laboratory at the price charged to Mayo Medical Laboratories. In addition, Mayo Medical Laboratories will charge an administrative fee per test for such referral services.

Reflex Testing
Mayo Medical Laboratories identifies tests that reflex when medically appropriate. In many cases, Mayo Medical Laboratories offers components of reflex tests individually as well as together. Clients should familiarize themselves with the test offerings and make a decision whether to order a reflex test or an individual component. Clients, who order a reflex test, can request to receive an “Additional Testing Notification Report” which indicates the additional testing that has been performed. This report will be faxed to the client. Clients who wish to receive the “Additional Testing Notification Report” should contact their Regional Manager or Regional Service Representative.

Reportable Disease
Mayo Medical Laboratories, in compliance with and adherence to the College of American Pathologists (CAP) Laboratory General Checklist (CAP GEN. 20373) strives to comply with laboratory reporting requirements for each state health department regarding reportable disease conditions. We report by mail, fax, and/or electronically, depending upon the specific state health department regulations. Clients shall be responsible for compliance with any state specific statutes concerning reportable conditions, including, but not limited to, birth defects registries or chromosomal abnormality registries. This may also include providing patient address/demographic information. Mayo Medical Laboratories’ reporting does not replace the client/physician responsibility to report as per specific state statues.

Request for Physician Name and Number
Mayo Medical Laboratories endeavors to provide high quality, timely results so patients are able to receive appropriate care as quickly as possible. While providing esoteric reference testing, there are times when we need to contact the ordering physician directly. The following are 2 examples:

When necessary to the performance of a test, the ordering physician’s name and phone number are requested as part of “Specimen Required.” This information is needed to allow our physicians to make timely consultations or seek clarification of requested services. If this information is not provided at the time of specimen receipt, we will call you to obtain the information. By providing this information up front, 

Master copies are retained online. Printed copies are considered current only on the date printed unless stamped Controlled.
delays in patient care are avoided.

In some situations, additional information from ordering physician is necessary to clarify or interpret a test result. At that time, Mayo Medical Laboratories will request physician’s name and phone number so that one of our staff can consult with the physician.

We appreciate your rapid assistance in supplying us with the ordering physician’s name and phone number when we are required to call. Working together, we can provide your patients with the highest quality testing services in the shortest possible time.

**Special Handling**

Mayo Medical Laboratories serves as a reference laboratory for clients around the country and world. Our test information, including days and time assays are performed as well as analytic turnaround time, is included under each test listing in the Test Catalog on mayomedicallaboratories.com. Unique circumstances may arise with a patient resulting in a physician request that the specimen or results receive special handling. There are several options available. These options can only be initiated by contacting Mayo Laboratory Inquiry at 800-533-1710 and providing patient demographic information.

There is a nominal charge associated with any special handling.

- **Hold:** If you would like to send us a specimen and hold that specimen for testing pending initial test results performed at your facility, please call Mayo Laboratory Inquiry. We will initiate a hold and stabilize the specimen until we hear from you.
- **Expedite:** If you would like us to expedite the specimen to the performing laboratory, you can call Mayo Laboratory Inquiry and request that your specimen be expedited. Once the shipment is received in our receiving area, we will deliver the specimen to the performing laboratory for the next scheduled analytic run. We will not set up a special run to accommodate an expedite request.
- **STAT:** In rare circumstances, STAT testing from the reference laboratory may be required for patients who need immediate treatment. These cases typically necessitate a special analytic run to turn results around as quickly as possible. To arrange STAT testing, please have your pathologist, physician, or laboratory director call Mayo Laboratory Inquiry. He/she will be connected with one of our medical directors to consult about the patient’s case. Once mutually agreed upon that there is a need for a STAT, arrangements will be made to assign resources to run the testing on a STAT basis when the specimen is received.

**Specimen Identification Policy**

In compliance with and adherence to the CAP and the Joint Commission’s 2008 Patient Safety Goals (1A), Mayo Medical Laboratories’ policy states that all specimens received for testing must be correctly and adequately labeled to assure positive identification. Specimens must have 2 person-specific identifiers on the patient label. Person-specific identifiers may include: accession number, patient’s first and last name, unique identifying number (eg, medical record number), or date of birth. Specimens are considered mislabeled when there is a mismatch between the person-specific identifiers on the specimen and information accompanying the specimen (eg, computer system, requisition form, additional paperwork).

When insufficient or inconsistent identification is submitted, Mayo Medical Laboratories will recommend that a new specimen be obtained, if feasible.

**Specimen Rejection**

All tests are unique in their testing requirements. To avoid specimen rejection or delayed turnaround times, please check the “Specimen Required” field within each test. You will be notified of rejected or problem specimens upon receipt.

Please review the following conditions prior to submitting a specimen to Mayo Medical Laboratories:
Specimen Volume
The “Specimen Required” section of each test includes 2 volumes - preferred volume and minimum volume. Preferred volume has been established to optimize testing and allows the laboratory to quickly process specimen containers, present containers to instruments, perform test, and repeat test, if necessary. Many of our testing processes are fully automated; and as a result, this volume allows hands-free testing and our quickest turnaround time (TAT). Since patient values are frequently abnormal, repeat testing, dilutions, or other specimen manipulations often are required to obtain a reliable, reportable result. Our preferred specimen requirements allow expeditious testing and reporting.

When venipuncture is technically difficult or the patient is at risk of complications from blood loss (eg, pediatric or intensive care patients), smaller volumes may be necessary. Specimen minimum volume is the amount required to perform an assay once, including instrument and container dead space.

When patient conditions do not mandate reduced collection volumes, we ask that our clients submit preferred volume to facilitate rapid, cost-effective, reliable test results. Submitting less than preferred volume may negatively impact quality of care by slowing TAT, increasing the hands-on personnel time (and therefore cost) required to perform test.

Mayo Clinic makes every possible effort to successfully test your patient’s specimen. If you have concerns about submitting a specimen for testing, please call Mayo Laboratory Inquiry at 800-533-1710 or 507-266-5700. Our staff will discuss the test and specimen you have available. While in some cases specimens are inadequate for desired test, in other cases, testing can be performed using alternative techniques.

Supplies
Shipping boxes, specimen vials, special specimen collection containers, and request forms are supplied without charge. Supplies can be requested using one of the following methods: use the online ordering functionality available at mayomedicallaboratories.com/supplies or call Mayo Laboratory Inquiry at 800-533-1710 or 507-266-5700.

Test Classifications
Analytical tests offered by Mayo Medical Laboratories are classified according to the FDA labeling of the test kit or reagents and their usage. Where appropriate, analytical test listings contain a statement regarding these classifications, test development, and performance characteristics. The classifications include:

- **FDA-PMI: FDA Cleared, Approved, or Exempt, Used Per Manufacturer’s Instructions** - This test has been cleared or approved by the U.S. Food and Drug Administration and is used per manufacturer’s instructions. Performance characteristics were verified by Mayo Clinic in a manner consistent with CLIA requirements.

- **M-LDT: Modified FDA Cleared or Approved Test** - This test has been modified from the
manufacturer’s instructions. Its performance characteristics were determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

- **ASR-LDT: Laboratory Developed Test Using an Analyte Specific Reagent** - This test was developed using an analyte specific reagent. Its performance characteristics were determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

- **LDT: Laboratory Developed Test** - This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

- **T-LDT: Laboratory Developed Test Using a Traditional Method** - This test uses a standard method. Its performance characteristics were determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

- **EUA: Emergency Use Authorization** - This test has received Emergency Use Authorization (EUA) by the U.S. Food and Drug Administration and is used per manufacturer's instructions. Performance characteristics were verified by Mayo Clinic in a manner consistent with CLIA requirements.

**Test Development Process**
Mayo Medical Laboratories serves patients and health care providers from Mayo Clinic, Mayo Health System, and our reference laboratory clients worldwide. We are dedicated to providing clinically useful, cost-effective testing strategies for patient care. Development, validation, and implementation of new and improved laboratory methods are major components of that commitment.

Each assay utilized at Mayo Clinic, whether developed on site or by others, undergoes an extensive validation and performance documentation period before the test becomes available for clinical use. Validations follow a standard protocol that includes:

- Accuracy
- Precision
- Sensitivity
- Specificity and interferences
- Reportable range
- Linearity
- Specimen stability
- Specimen type comparisons
- Urine preservative studies: stability at ambient, refrigerated, and frozen temperatures and with 7 preservatives; at 1, 3, and 7 days
- Comparative evaluation: with current and potential methods
- Reference values: using medically evaluated healthy volunteers, male and female, across age groups. The number of observations required for each test is determined by biostatistic analysis. Unless otherwise stated, reference values provided by Mayo Medical Laboratories are derived from studies performed in our laboratories. When reference values are obtained from other sources, the source is indicated in the “Reference Values” field.
- Workload recording
- Limitations of the assay
- Clinical utility and interpretation: written by Mayo Clinic medical experts, electronically available (MayoAccess™)
Test Result Call-Backs
Results will be phoned to a client when requested from the client (either on Mayo Medical Laboratories’ request form or from a phone call to Mayo Medical Laboratories from the client).

Time-Sensitive Specimens
Please contact Mayo Laboratory Inquiry at 800-533-1710 or 507-266-5700 prior to sending a specimen for testing of a time-sensitive nature. Relay the following information: facility name, account number, patient name and/or Mayo Medical Laboratories’ accession number, shipping information (ie, courier service, FedEx®, etc.), date to be sent, and test to be performed. Place specimen in a separate Mayo Medical Laboratories’ temperature appropriate bag. Please write “Expedite” in large print on outside of bag.

Turnaround Time (TAT)
Mayo Medical Laboratories’ extensive test menu reflects the needs of our own health care practice. We are committed to providing the most expedient TAT possible to improve diagnosis and treatment. We consider laboratory services as part of the patient care continuum wherein the needs of the patient are paramount. In that context, we strive to fulfill our service obligations. Our history of service and our quality metrics will document our ability to deliver on all areas of service including TAT.

Mayo Medical Laboratories defines TAT as the analytical test time (the time from which a specimen is received at the testing location to time of result) required. TAT is monitored continuously by each performing laboratory site within the Mayo Clinic Department of Laboratory Medicine and Pathology. For the most up-to-date information on TAT for individual tests, please visit us at mayomedicallaboratories.com or contact our Mayo Laboratory Inquiry at 800-533-1710 or 507-266-5700.

Unlisted Tests
Mayo Medical Laboratories does not list all available test offerings in the paper catalog. New procedures are developed throughout the year; therefore, some tests are not listed in this catalog. Although we do not usually accept referred tests of a more routine type, special arrangements may be made to provide your laboratory with temporary support during times of special need such as sustained instrumentation failure. For information about unlisted tests, please call Mayo Laboratory Inquiry at 800-533-1710 or 507-266-5700.
### RELATED DOCUMENTS

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### REVISION/DOCUMENT HISTORY

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<th>Version</th>
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<td>Created and assigned # 056279. Entered DLMP document control.</td>
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<tr>
<td>02/12/2018</td>
<td>002</td>
<td>Updated current test classifications, added section on extracted specimens per CAP MOL.32427, modified proficiency testing section</td>
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### REVIEW AND APPROVAL SIGNATURES

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1,25-Dihydroxyvitamin D, Serum

Clinical Information: Vitamin D is a generic designation for a group of fat-soluble, structurally similar sterols, which act as hormones. In the presence of renal disease or hypercalcemia, testing of 1,25-dihydroxy vitamin D (DHVD) might be needed to adequately assess vitamin D status. The 25-hydroxyvitamin D (25HDN) test (25HDN / 25-Hydroxyvitamin D2 and D3, Serum) in serum is otherwise the preferred initial test for assessing vitamin D status and most accurately reflects the body's vitamin D stores. Vitamin D compounds in the body are exogenously derived by dietary means; from plants as 25-hydroxyvitamin D2 (ergocalciferol or calciferol) or from animal products as 25-hydroxyvitamin D3 (cholecalciferol or calcidiol). Vitamin D may also be endogenously derived by conversion of 7-dihydrocholesterol to 25-hydroxyvitamin D3 in the skin upon ultraviolet exposure. 25HDN is subsequently formed by hydroxylation (CYP2R1) in the liver. 25HDN is a prohormone that represents the main reservoir and transport form of vitamin D, being stored in adipose tissue and tightly bound by a transport protein while in circulation. Biological activity is expressed in the form of DHVD, the active metabolite of 25HDN. 1-Alphahydroxylation (CYP27B1) occurs on demand, primarily in the kidneys, under the control of parathyroid hormone (PTH) before expressing biological activity. Like other steroid hormones, DHVD binds to a nuclear receptor, influencing gene transcription patterns in target organs. 25HDN may also be converted into the inactive metabolite 24,25-dihydroxyvitamin D (24,25D) by (CYP24A1) hydroxylation. This process, regulated by PTH, might increase DHVD synthesis at the expense of the alternative hydroxylation (CYP24A1) product 24,25D. Inactivation of 25HDN and DHVD by CYP24A1 is a crucial process that prevents over production of DHVD and resultant vitamin D toxicity. DHVD stimulates calcium absorption in the intestine and its production is tightly regulated through concentrations of serum calcium, phosphorus, and PTH. DHVD promotes intestinal calcium absorption and, in concert with PTH, skeletal calcium deposition, or less commonly, calcium mobilization. Renal calcium and phosphate reabsorption are also promoted, while prepro-PTH mRNA expression in the parathyroid glands is downregulated. The net result is a positive calcium balance, increasing serum calcium and phosphate levels, and falling PTH concentrations. In addition to its effects on calcium and bone metabolism, DHVD regulates the expression of a multitude of genes in many other tissues including immune cells, muscle, vasculature, and reproductive organs. DHVD levels are decreased in hypoparathyroidism and in chronic renal failure. DHVD levels may be high in primary hyperparathyroidism and in physiologic hyperparathyroidism secondary to low calcium or vitamin D intake. Some patients with granulomatous diseases (eg, sarcoidosis) and malignancies containing nonregulated 1-alpha hydroxylase in the lesion might have hypercalcemia that appears vitamin D mediated with normal or high serum phosphate (hyperphosphatemia) and hypercalcemia (both of which might be severe) in addition to low PTH and absent parathyroid hormone-related peptide (PTHRP). Assessment of 24,25D might also be required in patients with hypercalcemia that does not appear to be driven by PTH or PTHRP, and may be helpful in assessment of patients with loss of function inactivating CYP24A1 mutations. Differential diagnostic considerations include vitamin D intoxication and CYP24A1 deficiency.

Useful For: As a second-order test in the assessment of vitamin D status, especially in patients with renal disease. Investigation of some patients with clinical evidence of vitamin D deficiency (eg, vitamin D-dependent rickets due to hereditary deficiency of renal 1-alpha hydroxylase or end-organ resistance to 1,25-dihydroxyvitamin D). Differential diagnosis of hypercalcemia.

Interpretation: 1,25-Dihydroxyvitamin D (DVHD) concentrations are low in chronic renal failure and hypoparathyroidism. DVHD concentrations are high in sarcoidosis and other granulomatous diseases, some malignancies, primary hyperparathyroidism, and physiologic hyperparathyroidism. DVHD concentrations are not a reliable indicator of vitamin D toxicity; normal (or even low) results may be seen in such cases.

Reference Values:
Males:
- <16 years: 24-86 pg/mL
- > or =16 years: 18-64 pg/mL

Females:
- <16 years: 24-86 pg/mL
> or =16 years: 18-78 pg/mL

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.


11-Deoxycorticosterone, Serum

Clinical Information: The adrenal glands, ovaries, testes, and placenta produce steroid hormones, which can be subdivided into 3 major groups: mineral corticoids, glucocorticoids and sex steroids. Synthesis proceeds from cholesterol along 3 parallel pathways, corresponding to these 3 major groups of steroids, through successive side-chain cleavage and hydroxylation reactions. At various levels of each pathway, intermediate products can move into the respective adjacent pathways via additional, enzymatically catalyzed reactions (see Steroid Pathways in Special Instructions). 11-Deoxycorticosterone represents the last intermediate in the mineral corticoid pathway that has negligible mineral corticoid activity. It is converted by 11-beta-hydroxylase 2 (CYP11B2) or by 11-beta-hydroxylase 1 (CYP11B1) to the first mineral corticoids with significant activity, corticosterone. Corticosterone is in turn converted to 18-hydroxycorticosterone and finally to aldosterone, the most active mineral corticoid. Both of these reactions are catalyzed by CYP11B2, which, unlike its sister enzyme CYP11B1, also possesses 18-hydroxylase and 18-methyloxidase activity. The major diagnostic utility of measurement of steroid synthesis intermediates is in diagnosing disorders of steroid synthesis, in particular, congenital adrenal hyperplasia (CAH). All types of CAH are associated with cortisol deficiency with the exception of CYP11B2 deficiency and isolated impairments of the 17-lyase activity of CYP17A1 (this enzyme also has 17-alpha-hydroxylase activity). In cases of severe illness or trauma, CAH predisposes patients to poor recovery or death. Patients with the most common form of CAH (21-hydroxylase deficiency, >90% of cases), with the third most common form of CAH (3-beta-steroid dehydrogenase deficiency, <3% of cases), and those with the extremely rare StAR (steroidogenic acute regulatory protein) or 20,22 desmolase deficiencies, might also suffer mineral corticoid deficiency, as the enzyme blocks in these disorders are proximal to potent mineral corticoids. These patients might suffer salt-wasting crises in infancy. By contrast, patients with the second most common form of CAH, 11-hydroxylase deficiency (<5% of cases), are normotensive or hypertensive, as the block affects either CYP11B1 or CYP11B2, but rarely both, thus ensuring that at least corticosterone is still produced. In addition, patients with all forms of CAH might suffer the effects of substrate accumulation proximal to the enzyme block. In the 3 most common forms of CAH, the accumulating precursors spill over into the sex steroid pathway, resulting in virilization of females or, in milder cases, in hirsutism, polycystic ovarian syndrome, or infertility, as well as in possible premature adrenarche and pubarche in both genders. Measurement of the various precursors of mature mineral corticoids and glucocorticoids, in concert with the determination of sex steroid concentrations, allows diagnosis of CAH and its precise type, and serves as an aid in monitoring steroid replacement therapy and other therapeutic interventions. Measurement of 11-deoxycorticosterone and its glucocorticoid pendant, 11-deoxycortisol (also known as compound S), is aimed at diagnosing: -CYP11B1 deficiency (associated with cortisol deficiency) -The rarer CYP11B2 deficiency (no cortisol deficiency) -The yet less common glucocorticoid-responsive hyperaldosteronism (where expression of the gene CYP11B1 is driven by the CYP11B1 promoter, thus making it responsive to adrenocorticotropic hormone: ACTH rather than renin) For other forms of CAH, the following tests might be relevant: -11-Hydroxylase deficiency: - DOC / 11-Deoxycortisol, Serum - CORTC / Corticosterone, Serum - HYD18 / Hydroxycorticosterone, 18 - PRA / Renin Activity, Plasma - ALDS / Aldosterone, Serum -3-Beta-steroid-dehydrogenase deficiency: - 17PRN / Pregnenolone and 17-Hydroxypregnenolone -17-Hydroxylase deficiency or 17-lyase deficiency (CYP17A1 has both activities): - PREGN / Pregnenolone, Serum - 17OHP / 17-Hydroxyprogrenolone, Serum - PGSN / Progesterone, Serum - OHPG / 17-Hydroxyprogesterone, Serum - DHEA / Dehydroepiandrosterone (DHEA), Serum - ANST / Androstenedione, Serum Cortisol should be measured in all cases of suspected CAH. In the diagnosis of
suspected 11-hydroxylase deficiency and glucocorticoid-responsive hyperaldosteronism, this test should be used in conjunction with measurements of 11-deoxycortisol, corticosterone, 18-hydroxycorticosterone, cortisol, renin, and aldosterone.

**Useful For:** Diagnosis of suspected 11-hydroxylase deficiency, including the differential diagnosis of 11 beta-hydroxylase 1 (CYP11B1) versus 11 beta-hydroxylase 2 (CYP11B2) deficiency, and in the diagnosis of glucocorticoid-responsive hyperaldosteronism Evaluating congenital adrenal hyperplasia newborn screen-positive children, when elevations of 17-hydroxyprogesterone are only moderate, suggesting possible 11-hydroxylase deficiency

**Interpretation:** In 11 beta-hydroxylase 1 (CYP11B1) deficiency, serum concentrations of cortisol will be low (usually <7 microgram/dL for a morning draw). 11-Deoxycortisol and 11-deoxycorticosterone are elevated, usually to at least 2 to 3 times (more typically 20-300 times) the upper limit of the normal reference range on a morning blood draw. Elevations in 11-deoxycortisol are usually relatively greater than those of 11-deoxycorticosterone, because of the presence of intact 11 beta-hydroxylase 2 (CYP11B2). For this reason, serum concentrations of all potent mineral corticoids (corticosterone, 18-hydroxycorticosterone, and aldosterone) are typically increased above the normal reference range. Plasma renin activity is correspondingly low or completely suppressed. Caution needs to be exercised in interpreting the mineral corticoid results in infants younger than 7 days; mineral corticoid levels are often substantially elevated in healthy newborns in the first few hours of life and only decline to near-adult levels by week 1. Mild cases of CYP11B1 deficiency might require adrenocorticotrophic hormone (ACTH)1-24 stimulation testing for definitive diagnosis. In affected individuals, the observed serum 11-deoxycortisol concentration 60 minutes after intravenous or intramuscular administration of 250 microgram of ACTH1-24 will usually exceed 20 ng/mL, or demonstrate at least a 4-fold rise. Such increments are rarely, if ever, observed in unaffected individuals. The corresponding cortisol response will be blunted (<18 ng/mL peak). In CYP11B2 deficiency, serum cortisol concentrations are usually normal, including a normal response to ACTH1-24. 11-Deoxycorticosterone will be elevated, often more profoundly than in CYP11B1 deficiency, while 11-deoxycortisol may or may not be significantly elevated. Serum corticosterone concentrations can be low, normal, or slightly elevated, while serum 18-hydroxycorticosterone and aldosterone concentrations will be low in the majority of cases. However, if the underlying genetic defect has selectively affected 18-hydroxylase activity, corticosterone concentrations will be substantially elevated. Conversely, if the deficit affects aldosterone synthase function primarily, 18-hydroxycorticosterone concentrations will be very high. Expression of the CYP11B2 gene is normally regulated by renin and not ACTH. In glucocorticoid-responsive hyperaldosteronism, the ACTH-responsive promoter of CYP11B1 exerts aberrant control over CYP11B2 gene expression. Consequently, corticosterone, 18-hydroxycorticosterone, and aldosterone are significantly elevated in these patients and their levels follow a diurnal pattern, governed by the rhythm of ACTH secretion. In addition, the high levels of CYP11B2 lead to 18-hydroxylation of 11-deoxycortisol (an event that is ordinarily rare, as CYP11B1, which has much greater activity in 11-deoxycortisol conversion than CYP11B2, lacks 18-hydroxylation activity). Consequently, significant levels of 18-hydroxycortisol, which normally is only present in trace amounts, might be detected in these patients. Ultimate diagnostic confirmation comes from showing direct responsiveness of mineral corticoid production to ACTH1-24 injection. Normally, this has little if any effect on corticosterone, 18-hydroxycorticosterone, and aldosterone levels. This testing may then be further supplemented by showing that mineral corticoid levels fall after administration of dexamethasone. Sex steroid levels are moderately to significantly elevated in CYP11B1 deficiency and much less, or minimally, pronounced in CYP11B2 deficiency. Sex steroid levels in glucocorticoid-responsive hyperaldosteronism are usually normal. Most untreated patients with 21-hydroxylase deficiency have serum 17-hydroxyprogesterone concentrations well in excess of 1,000 ng/dL. For the few patients with levels in the range of higher than 630 ng/dL (upper limit of reference range for newborns) to 2,000 or 3,000 ng/dL, it might be prudent to consider 11-hydroxylase deficiency as an alternative diagnosis. This is particularly true if serum androstenedione concentrations are also only mildly to modestly elevated, and if the phenotype is not salt wasting but either simple virilizing (female) or normal (female or male). 11-Hydroxylase deficiency, in particular if it affects CYP11B1, can be associated with modest elevations in serum 17-hydroxyprogesterone concentrations. In these cases, testing for CYP11B1 deficiency and CYB11B2 deficiency should be considered and interpreted as described above. Alternatively, measurement of 21-deoxycortisol might
be useful. This minor pathway metabolite accumulates in CYP21A2 deficiency, as it requires 21-hydroxylation to be converted to cortisol, but is usually not elevated in CYP11B1 deficiency, since its synthesis requires via 11-hydroxylation of 17-hydroxyprogesterone.

**Reference Values:**
- < or =18 years: <30 ng/dL
- >18 years: <10 ng/dL

**Clinical References:**

**11-Deoxycortisol, Serum**

**Clinical Information:** 11-Deoxycortisol (Compound S) is the immediate precursor of cortisol: 11 beta-hydroxylation 11-deoxycortisol--------------------------->cortisol Compound S is typically increased when adrenocorticotropic hormone (ACTH) levels are increased (eg, Cushing disease, ACTH-producing tumors) or in 11 beta-hydroxylation deficiency, a rare subtype of congenital adrenal hyperplasia (CAH). In CAH due to 11 beta-hydroxylation deficiency, cortisol levels are low, resulting in increased pituitary ACTH production and increased serum and urine 11-deoxycortisol levels. Pharmacological blockade of 11 beta-hydroxylation with metyrapone can be used to assess the function of the hypothalamic-pituitary-adrenal axis (HPA). In this procedure metyrapone is administered to patients, and serum 11-deoxycortisol levels or urinary 17-hydroxy steroid levels are measured either at baseline (midnight) and 8 hours later (overnight test), or at baseline and once per day during a 2-day metyrapone test (4-times a day metyrapone administration over 2 days). Two-day metyrapone testing has been largely abandoned because of the logistical problems of multiple timed urine and blood collections and the fact that overnight testing provides very similar results. In either case, the normal response to metyrapone administration is a fall in serum cortisol levels, triggering a rise in pituitary ACTH secretion, which, in turn, leads to a rise in 11-deoxycortisol levels due to the ongoing 11-deoxycortisol-to-cortisol conversion block. In the diagnostic workup of suspected adrenal insufficiency, the results of overnight metyrapone testing correlate closely with the gold standard of HPA-axis assessment, insulin hypoglycemia testing. Combining 11-deoxycortisol measurements with ACTH measurements during metyrapone testing further enhances the performance of the test. Impairment of any component of the HPA-axis results in a subnormal response to metyrapone stimulation testing. By contrast, standard-dose or low-dose ACTH(1-24) (cosyntropin)-stimulation testing, which forms the backbone for diagnosis of primary adrenal failure (Addison disease), only assess the ability of the adrenal cells to respond to ACTH stimulation. While this allows unequivocal diagnosis of primary adrenal failure, in the setting of secondary or tertiary adrenal insufficiency, metyrapone testing is more sensitive and specific than either standard-dose or low-dose ACTH(1-24)-stimulation testing. Metyrapone testing is also sometimes employed in the differential diagnosis of Cushing syndrome. In Cushing disease (pituitary-dependent ACTH overproduction), the ACTH-hypersecreting pituitary tissue remains responsive to the usual feedback stimuli, just at a higher "set-point" than in the normal state, resulting in increased ACTH secretion and 11-deoxycortisol production after metyrapone administration. By contrast, in Cushing syndrome due to primary adrenal corticosteroid oversecretion or ectopic ACTH secretion, pituitary ACTH production is appropriately shut down and there is usually no further rise in ACTH and, hence 11-deoxycortisol, after metyrapone administration. The metyrapone test has similar sensitivity and specificity to the high-dose dexamethasone suppression test in the differential diagnosis of Cushing disease, but is less widely used because of the lack of availability of an easy, automated 11-deoxycortisol assay. In recent years, both tests...
have been supplanted to some degree by corticotropin-releasing hormone (CRH)-stimulation testing with petrosal sinus serum ACTH sampling. See Steroid Pathways in Special Instructions.

**Useful For:** Diagnostic workup of patients with congenital adrenal hyperplasia Part of metyrapone testing in the workup of suspected secondary or tertiary adrenal insufficiency Part of metyrapone testing in the differential diagnostic workup of Cushing syndrome

**Interpretation:** In a patient suspected of having congenital adrenal hyperplasia (CAH), elevated serum 11-deoxycortisol levels indicate possible 11 beta-hydroxylase deficiency. However, not all patients will show baseline elevations in serum 11-deoxycortisol levels. In a significant proportion of cases, increases in 11-deoxycortisol levels are only apparent after adrenocorticotropic hormone (ACTH)(1-24) stimulation.(1) Serum 11-deoxycortisol levels below 1,700 ng/dL 8 hours after metyrapone administration is indicative of probable adrenal insufficiency. The test cannot reliably distinguish between primary and secondary or tertiary causes of adrenal failure, as neither patients with pituitary failure, nor those with primary adrenocortical failure, tend to show an increase of 11-deoxycortisol levels after metyrapone is administered. See Steroid Pathways in Special Instructions.

**Reference Values:**
- < or =18 years: <344 ng/dL
- >18 years: 10-79 ng/dL

For SI unit Reference Values, see [https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html](https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html).

**Clinical References:**

**FDOSOX**

**11-Desoxycortisol (Specific Compound S)**

**Reference Values:**

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**THCMX**

**11-nor-Delta-9-Tetrahydrocannabinol-9-Carboxylic Acid (Carboxy-THC) Confirmation, Chain of Custody, Meconium**

**Clinical Information:** Marijuana and other psychoactive products obtained from the plant Cannabis sativa are the most widely used illicit drugs in the world.(1) Marijuana has unique behavioral effects that include feelings of euphoria and relaxation, altered time perception, impaired learning and memory, lack of concentration, and mood changes (eg, panic reactions and paranoia). Cannabis sativa produces numerous compounds collectively known as cannabinoids including delta-9-tetrahydrocannabinol.
(THC), which is the most prevalent and produces most of the characteristic pharmacological effects of smoked marijuana. THC undergoes rapid hydroxylation by the cytochrome (CYP) enzyme system to form the active metabolite 11-hydroxy-THC. Subsequent oxidation of 11-hydroxy-THC produces the inactive metabolite 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH; carboxy-THC). THC-COOH and its glucuronide conjugate have been identified as the major end-products of metabolism. THC is highly lipid soluble, resulting in its concentration and prolonged retention in fat tissue. Cannabinoids cross the placenta, but a dose-response relationship or correlation has not been established between the amount of marijuana use in pregnancy and the levels of cannabinoids found in meconium, the first fecal matter passed by the neonate. The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing amniotic fluid. The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation. Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection of in utero drug exposure up to 5 months before birth

**Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

**Interpretation:** The presence of 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid > or =10 ng/g is indicative of in utero drug exposure up to 5 months before birth.

**Reference Values:**

- Negative
- Positives are reported with a quantitative LC-MS/MS result.
- Cutoff concentrations
  - Tetrahydrocannabinol carboxylic acid (marijuana metabolite) by LC-MS/MS: 10 ng/g

**Clinical References:**
which is the most prevalent and produces most of the characteristic pharmacological effects of smoked marijuana. (2) THC undergoes rapid hydroxylation by the cytochrome (CYP) enzyme system to form the active metabolite 11-hydroxy-THC. Subsequent oxidation of 11-hydroxy-THC produces the inactive metabolite 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH; carboxy-THC). THC-COOH and its glucuronide conjugate have been identified as the major end-products of metabolism. THC is highly lipid soluble, resulting in its concentration and prolonged retention in fat tissue. (3)

Cannabinoids cross the placenta, but a dose-response relationship or correlation has not been established between the amount of marijuana use in pregnancy and the levels of cannabinoids found in meconium, the first fecal matter passed by the neonate. (4,5) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing amniotic fluid. (5) The first evidence of meconium in the fetal intestine appears at approximately the tenth to twelfth week of gestation, and slowly moves into the colon by the sixteenth week of gestation. (6) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis. (5)

**Useful For:** Detection of in utero drug exposure to marijuana (tetrahydrocannabinol) up to 5 months before birth

**Interpretation:** The presence of 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid at 10 ng/g or greater is indicative of in utero drug exposure up to 5 months before birth.

**Reference Values:**

Negative

Positives are reported with a quantitative LC-MS/MS result.

Cutoff concentrations

Tetrahydrocannabinol carboxylic acid (marijuana metabolite) by LC-MS/MS: 10 ng/g

**Clinical References:**


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**14-3-3 Protein, Spinal Fluid**

**Clinical Information:** The 14-3-3 proteins are a group of highly conserved proteins composed of several isoforms that are involved in the regulation of protein phosphorylation and mitogen-activated protein kinase pathways. They exist in vivo as dimers of the various isoforms with apparent molecular mass of 30 kDa on sodium dodecyl sulfate polyacrylamide gel electrophoresis and 60 kDa on gel chromatography. Sequence homology among the various isoforms ranges from 22% to 100%. The beta, gamma, and theta isoforms are found in tissues of the nervous system. Detectable 14-3-3 protein in the cerebrospinal fluid (CSF) is indicative of substantial, relatively rapid neuronal destruction. Increased CSF concentrations of 14-3-3 proteins have been described in patients with various forms of Creutzfeldt-Jakob disease (CJD), some other rapidly progressive dementias, and a large range of other vascular, inflammatory, neoplastic, and metabolic central nervous system (CNS) disorders (see Cautions), which can be associated with significant and rapid neuronal destruction. The main clinical use of 14-3-3 measurements is in the differential diagnosis of dementia, in particular to distinguish CJD and its variants from other dementias. The most common forms of dementia (progressive multi-infarct dementia and Alzheimer disease) are uncommonly associated with elevated CSF levels of 14-3-3,
presumably because of their slow pace of progression. CJD is an incurable neurodegenerative disease caused by accumulation of self-catalytically malfolded endogenous prion proteins in the CNS. Its cause is most commonly sporadic, but it can be inherited (mutations that predispose to malfolding) or acquired (iatrogenic transmission by infected human tissues or tissue extracts or surgical procedures, or by ingestion of some animal products that contain malfolded prion proteins). The diagnosis of CJD is highly complex and involves clinical history and neurologic examination, electroencephalographs (EEG), magnetic resonance imaging (MRI), and exclusion of other possible causes of dementia, in addition to CSF examination. Several, slightly different scoring systems are in use to integrate these parameters into a final diagnosis of possible, probable, or definite CJD. The most widely accepted of these scoring systems is the WHO set of diagnostic criteria for sporadic CJD from 1998 (see Interpretation).

Useful For: Supporting, in conjunction with other tests, a diagnosis of Creutzfeldt-Jakob disease in patients with rapidly progressive dementia when other neurodegenerative conditions have been excluded.

Interpretation: A concentration of 14-3-3 protein in cerebrospinal fluid (CSF) of 2.0 ng/mL or higher supports the diagnosis of Creutzfeldt-Jakob disease (CJD) in patients who have been carefully preselected based on various diagnostic criteria. CSF 14-3-3 measurement is particularly helpful in sporadic CJD, where it is used as one of several diagnostic criteria. Sporadic CJD World Health Organization (WHO) diagnostic criteria from 1998: 1. Definitive CJD: -Neuropathological diagnosis by standard techniques AND/OR immunohistochemistry AND/OR Western blot confirmed protease-resistant prion protein AND/OR presence of scrapie-associated fibrils 2. Probable CJD: -Progressive dementia -At least 2 of the following symptoms: -Myoclonus, pyramidal/extrapyramidal, visual or cerebellar, akinetic mutism -Positive electroencephalographs (EEG) (periodic epileptiform discharges) AND/OR positive CSF 14-3-3 protein and less than 2 years disease duration -No alternate diagnosis 3. Possible CJD: -Progressive dementia -At least 2 of the following symptoms: -Myoclonus, pyramidal/extrapyramidal, visual or cerebellar, akinetic mutism -No supportive EEG and less than 2 years disease duration Recently proposed, but not yet universally accepted, amendments to these criteria center on including magnetic resonance imaging (MRI) high-signal abnormalities in caudate nucleus and/or putamen on diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR) as diagnostic criteria for probable CJD. The USA Center of Disease Control and Prevention supports these modified WHO criteria as of 2010 (http://www.cdc.gov/ncidod/dvrd/cjd/diagnostic_criteria.html). There is no established role for 14-3-3 measurement in the diagnosis of acquired or inherited CJD.

Reference Values:
Normal: < or =2.0 ng/mL
Elevated: >2.0 ng/mL


17OHP
17-Hydroxyprogrenenolone, Serum

Clinical Information: Congenital adrenal hyperplasia (CAH) is caused by inherited defects in steroid biosynthesis. Deficiencies in several enzymes cause CAH including 21-hydroxylase (CYP21A2 mutations; 90% of cases), 11-hydroxylase (CYP11A1 mutations; 5%-8%), 3-beta-hydroxy dehydrogenase (HSD3B2 mutations; <5%), and 17-alpha-hydroxylase (CYP17A1 mutations; 125 cases reported to date). The resulting hormone imbalances (reduced glucocorticoids and mineralocorticoids, and elevated steroid
intermediates and androgens) can lead to life-threatening, salt-wasting crises in the newborn period and incorrect gender assignment of virilized females. The adrenal glands, ovaries, testes, and placenta produce steroid intermediates, which are hydroxylated at the position 21 (by 21-hydroxylase) and position 11 (by 11-hydroxylase) to produce cortisol. Deficiency of either 21-hydroxylase or 11-hydroxylase results in decreased cortisol synthesis and loss of feedback inhibition of adrenocorticotropic hormone (ACTH) secretion. The consequent increased pituitary release of ACTH drives increased production of steroid intermediates. The steroid intermediates are oxidized at position 3 (by 3-beta-hydroxy dehydrogenase: 3-beta-HSD). The 3-beta-HSD enzyme allows formation of 17-hydroxyprogesterone (17-OHPG) from 17-hydroxypregnenolone and progesterone from pregnenolone. When 3-beta-HSD is deficient, cortisol is decreased, 17-hydroxypregnenolone and pregnenolone levels may increase, and 17-OHPG and progesterone levels, respectively, are low. Dehydroepiandrosterone (DHEA) is also converted to androstenedione by 3-beta-HSD and may be elevated in patients affected with 3-beta-HSD deficiency. The best screening test for CAH, most often caused by either 21- or 11-hydroxylase deficiency, is the analysis of 17-hydroxyprogesterone (along with cortisol and androstenedione). CAH21 / Congenital Adrenal Hyperplasia (CAH) Profile for 21-Hydroxylase Deficiency allows the simultaneous determination of these 3 analytes. Alternatively, these tests may be ordered individually: OHPG / 17-Hydroxyprogesterone, Serum; CINP / Cortisol, Serum, LC-MS/MS; and ANST / Androstenedione, Serum. If both 21- and 11-hydroxylase deficiency have been ruled out, analysis of 17-hydroxypregnenolone and pregnenolone may be used to confirm the diagnosis of 3-beta-HSD or 17-alpha-hydroxylase deficiency. See Steroid Pathways in Special Instructions.

**Useful For:** As an ancillary test for congenital adrenal hyperplasia (CAH), particularly in situations in which a diagnosis of 21-hydroxylase and 11-hydroxylase deficiency have been ruled out Confirming a diagnosis of 3-beta-hydroxy dehydrogenase (3-beta-HSD) deficiency Analysis for 17-hydroxypregnenolone is also useful as part of a battery of tests to evaluate females with hirsutism or infertility; both can result from adult-onset CAH.

**Interpretation:** Diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always requires the measurement of several steroids. Patients with CAH due to steroid 21-hydroxylase gene (CYP21A2) mutations usually have very high levels of androstenedione, often 5-fold to 10-fold elevations. 17-hydroxyprogesterone (17-OHPG) levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. For the HSD3B2 mutation, cortisol, 17-OHPG and progesterone levels will be will be decreased; 17-hydroxypregnenolone and pregnenolone and dehydroepiandrosterone (DHEA) levels will be increased. In the much less common CYP11A1 mutation, androstenedione levels are elevated to a similar extent as in CYP21A2 mutation, and cortisol is also low, but OHPG is only mildly, if at all, elevated. In the also very rare 17-alpha-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxypregnenolone, OHPG, dehydroepiandrosterone sulfate), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid and its precursors (in particular pregnenolone, 11-dexycorticosterone, corticosterone, and 18-hydroxycorticosterone) are increased. See Steroid Pathways in Special Instructions.

**Reference Values:**

**CHILDREN***

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<tr>
<td>Premature (26-28 weeks): 1,219-9,799 ng/dL</td>
<td></td>
</tr>
<tr>
<td>Premature (29-36 weeks): 346-8,911 ng/dL</td>
<td></td>
</tr>
<tr>
<td>Full term (1-5 months): 229-3,104 ng/dL</td>
<td></td>
</tr>
<tr>
<td>6 months-364 days: 221-1,981 ng/dL</td>
<td></td>
</tr>
<tr>
<td>1-2 years: 35-712 ng/dL</td>
<td></td>
</tr>
<tr>
<td>3-6 years: &lt;277 ng/dL</td>
<td></td>
</tr>
<tr>
<td>7-9 years: &lt;188 ng/dL</td>
<td></td>
</tr>
<tr>
<td>10-12 years: &lt;393 ng/dL</td>
<td></td>
</tr>
<tr>
<td>13-15 years: 35-465 ng/dL</td>
<td></td>
</tr>
<tr>
<td>16-17 years: 32-478 ng/dL</td>
<td></td>
</tr>
</tbody>
</table>

**TANNER STAGES**

| Stage I: <209 ng/dL |          |
Stage II: <356 ng/dL  
Stage III: <451 ng/dL  
Stage IV-V: 35-478 ng/dL

Female Premature (26-28 weeks): 1,219-9,799 ng/dL  
Premature (29-36 weeks): 346-8,911 ng/dL  
Full term (1-5 months): 229-3,104 ng/dL  
6 months-364 days: 221-1,981 ng/dL  
1-2 years: 35-712 ng/dL  
3-6 years: <277 ng/dL  
7-9 years: <213 ng/dL  
10-12 years: <399 ng/dL  
13-15 years: <408 ng/dL  
16-17 years: <424 ng/dL

TANNER STAGES
Stage I: <236 ng/dL  
Stage II: <368 ng/dL  
Stage III: <431 ng/dL  
Stage IV-V: <413 ng/dL

Adults
Males  
> or =18 years: 55-455 ng/dL
Females  
> or =18 years: 31-455 ng/dL


Clinical References:  

17-Hydroxyprogesterone, Serum

Clinical Information: Congenital adrenal hyperplasia (CAH) is caused by inherited defects in steroid biosynthesis. The resulting hormone imbalances with reduced glucocorticoids and mineralocorticoids and elevated 17-hydroxyprogesterone (OHPG) and androgens can lead to life-threatening, salt-wasting crisis in the newborn period and incorrect gender assignment of virilized females. Adult-onset CAH may result in hirsutism or infertility in females. The adrenal glands, ovaries, testes, and placenta produce OHPG. It is hydroxylated at the 11 and 21 position to produce cortisol. Deficiency of either 11- or 21-hydroxylase results in decreased cortisol synthesis, and feedback inhibition of adrenocorticotropic hormone (ACTH) secretion is lost. Consequent increased pituitary release of ACTH increases production of OHPG. But, if 17-alpha-hydroxylase (which allows formation of OHPG from progesterone) or 3-beta-hydroxysteroid dehydrogenase type 2 (which allows formation of 17-hydroxyprogesterone formation from 17-hydroxypregnenolone) are deficient, OHPG levels are low with possible increase in progesterone or pregnenolone respectively. OHPG is bound to both corticosteroid binding globulin and albumin and total OHPG is measured in this assay. OHPG is converted to pregnanetriol, which is conjugated and excreted in the urine. In all instances, more specific tests are available to diagnose
disorders or steroid metabolism than pregnanetriol measurement. Most (90%) cases of CAH are due to mutations in the steroid 21-hydroxylase gene (CYP21A2). CAH due to 21-hydroxylase deficiency is diagnosed by confirming elevations of OHPG and androstenedione (ANST / Androstenedione, Serum) with decreased cortisol (CINP / Cortisol, Serum, LC-MS/MS). By contrast, in 2 less common forms of CAH, due to 17-hydroxylase or 11-hydroxylase deficiency, OHPG and androstenedione levels are not significantly elevated and measurement of progesterone (PGSN / Progesterone, Serum) and deoxycorticosterone (FDOC / Deoxycorticosterone [DOC], Serum), respectively, are necessary for diagnosis. CAH21 / Congenital Adrenal Hyperplasia (CAH) Profile for 21-Hydroxylase Deficiency allows the simultaneous determination of OHPG, androstenedione, and cortisol. See Steroid Pathways in Special Instructions.

Useful For: The analysis of 17-hydroxyprogesterone (17-OHPG) is 1 of the 3 analytes along with cortisol and androstenedione, that constitutes the best screening test for congenital adrenal hyperplasia (CAH), caused by either 11- or 21-hydroxylase deficiency. Analysis for 17-OHPG is also useful as part of a battery of tests to evaluate females with hirsutism or infertility; both can result from adult-onset CAH.

Interpretation: Diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always requires the measurement of several steroids. Patients with CAH due to steroid 21-hydroxylase gene (CYP21A2) mutations usually have very high levels of androstenedione, often 5- to 10-fold elevations. 17-hydroxyprogesterone (OHPG) levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. In the much less common CYP11A1 mutation, androstenedione levels are elevated to a similar extent as in CYP21A2 mutation, and cortisol is also low, but OHPG is only mildly, if at all, elevated. In the also very rare 17-alpha-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxypregnenolone, OHPG, dehydroepiandrosterone sulfate), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid and its precursors, in particular progesterone, 11-deoxycorticosterone, and 18-hydroxydeoxycorticosterone, are increased. The goal of CAH treatment is normalization of cortisol levels and ideally also of sex-steroid levels. Traditionally, OHPG and urinary pregnanetriol or total ketosteroid excretion are measured to guide treatment, but these tests correlate only modestly with androgen levels. Therefore, androstenedione and testosterone should also be measured and used to guide treatment modifications. Normal prepubertal levels may be difficult to achieve, but if testosterone levels are within the reference range, androstenedione levels of up to 100 ng/dL are usually regarded as acceptable. See Steroid Pathways in Special Instructions.

Reference Values:
Children
   Preterm infants
     Preterm infants may exceed 630 ng/dL, however, it is uncommon to see levels reach 1,000 ng/dL.
   Term infants
     0-28 days: <630 ng/dL
     Levels fall from newborn (<630 ng/dL) to prepubertal gradually within 6 months.
   Prepubertal males: <110 ng/dL
   Prepubertal females: <100 ng/dL
Adults
   Males: <220 ng/dL
   Females
     Follicular: <80 ng/dL
     Luteal: <285 ng/dL
   Postmenopausal: <51 ng/dL


**GLIOF 35272**

### 1p/19q Deletion in Gliomas, FISH, Tissue

**Clinical Information:** Astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas are the major histologic types of human gliomas; histologic differentiation among these tumors can be difficult. It has been shown that specific genetic alterations are highly associated with specific morphologic types of gliomas. In addition, specific genetic alterations seem to predict prognosis (survival), as well as response to specific chemotherapeutic and radiotherapeutic regimens, irrespective of tumor morphology. Deletions of the short arm of chromosome 1(1p) and long arm of chromosome 19 (19q), are strongly correlated with gliomas of oligodendrogial morphology. Approximately 70%, 50%, and 50% of oligodendrogliomas have deletions of 19q, 1p, and of both 19q and 1p, respectively. Combined 1p and 19q loss is infrequent in gliomas of astrocytic origin. Thus, the presence of combined 1p/19q loss is strongly suggestive that a glioma is of oligodendroglioma lineage. Gains of chromosome 19 and of the 19 q-arm are associated with gliomas of astrocytic origin. Deletions of 1p and of both 1p and 19q also have been associated with response to various chemotherapeutic and radiotherapeutic regimens. These responses have been especially associated with high-grade oligodendrogliomas (anaplastic oligodendrogliomas). Chromosomal microarray (CMA/ Chromosomal Microarray, Tumor, Formalin-Fixed Paraffin-Embedded), rather than FISH, may be of benefit to evaluate for acquired alterations associated with the molecular classification of glioma.(1) See Cytogenetic Analysis of Glioma in Special Instructions.

**Useful For:** Aids in diagnosing oligodendroglioma tumors and predicting the response of an oligodendroglioma to therapy May be useful in tumors with a complex "hybrid" morphology requiring differentiation from pure astrocytomas to support the presence of oligodendrogial differentiation/lineage Indicated when a diagnosis of oligodendroglioma, both low-grade World Health Organization (WHO, grade II) and anaplastic (WHO, grade III) is rendered Strongly recommended when a diagnosis of mixed oligoastrocytomas is rendered

**Interpretation:** The presence of 1p deletion and combined 1p and 19q deletion supports a diagnosis of oligodendroglioma may indicate that the patient may respond to chemotherapy and radiation therapy. The presence of gain of chromosome 19 supports a diagnosis of high-grade astrocytoma (glioblastoma multiforme). A negative result does not exclude a diagnosis of oligodendroglioma or high-grade astrocytoma.

**Reference Values:** An interpretive report will be provided.

Clinical Information: Erythrocytosis (ie, increased RBC mass and elevated hemoglobin and hematocrit) may be primary, due to an intrinsic defect of bone marrow stem cells as in polycythemia vera (PV), or secondary, in response to increased serum erythropoietin (Epo) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide, cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other Epo-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanism may be suspected. Unlike PV, hereditary erythrocytosis is not associated with the risk of clonal evolution and most commonly presents as isolated erythrocytosis that has been present since childhood. Hereditary erythrocytosis may be caused by mutations in one of several genes and inherited in either an autosomal dominant or autosomal recessive manner. Genetic mutations causing hereditary erythrocytosis have been found in genes coding for alpha and beta hemoglobins, hemoglobin stabilization proteins (eg, 2,3-bisphosphoglycerate mutase: BPGM), the erythropoietin receptor (EPOR), and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF, prolyl hydroxylase domain: PHD, and von Hippel Lindau: VHL), see table. High-oxygen-affinity hemoglobin variants and BPGM abnormalities result in a decreased p50 result, whereas those affecting EPOR, HIF, PHD, and VHL have normal p50 results. The true prevalence of mutations causing hereditary erythrocytosis is unknown; however, very few cases of 2,3-BPG deficiency-associated hereditary erythrocytosis have been identified and this disorder is thought to be rare. Erythrocytosis Testing Gene Inheritance Serum Epo p50 JAK2 V617F Acquired Decreased Normal JAK2 exon 12 Acquired Decreased Normal EPOR Dominant Decreased Normal PHD2/EGLN1 Dominant Normal Normal to mildly decreased BPGM Recessive Normal Decreased Beta Globin Dominant Normal to increased Decreased Alpha Globin Dominant Normal to increased Decreased HIF2A/EPAS1 Dominant Normal to increased Normal VHL Recessive Normal to increased Normal

Useful For: Diagnosis of 2,3-bisphosphoglycerate mutase deficiency in individuals with lifelong, unexplained erythrocytosis Identifying mutation carriers in family members of an affected individual for the purposes of preconception genetic counseling

Interpretation: An interpretive report will be provided and will include specimen information, assay information, and whether the specimen was positive for any mutations in the gene. If positive, the mutation will be correlated with clinical significance, if known.

Reference Values: An interpretive report will be provided.

2,3-Dinor-11Beta-Prostaglandin F2 Alpha, Urine

**Clinical Information:** 2,3-Dinor-11beta-prostaglandin F2 alpha is the most abundant metabolic product of prostaglandins released by activated mast cells. Systemic mastocytosis (SM) is a disease in which clonally derived mast cells accumulate in peripheral tissues. Degranulation of these mast cells releases large amounts of histamines, prostaglandins, leukotrienes, and tryptase. World Health Organization diagnostic criteria for SM require the presence of elevated mast cell counts on a bone marrow biopsy and 1 of the following minor criteria: abnormal mast cell morphology, KIT Asp816Val mutation, CD25-positive mast cells, or serum tryptase greater than 20 ng/mL. Alternatively, SM diagnosis can be made with the presence of 3 minor criteria in the absence of abnormal bone marrow studies. Measurement of mast cell mediators in blood or urine is less invasive and is advised for the initial evaluation of suspected cases. Elevated levels of serum tryptase, urinary N-methylhistamine (NMH), 2,3-dinor-11beta-prostaglandin F2 alpha (2,3 BPG), or leukotriene E4 (LTE4) are consistent with the diagnosis of systemic mast cell disease.

**Useful For:** Screening for mast cell activation disorders including systemic mastocytosis

**Interpretation:** Elevated urine 2,3-dinor-11beta-prostaglandin F2 alpha is consistent with systemic mastocytosis.

**Reference Values:**
<5,205 pg/mg creatinine

**Clinical References:**

21-Deoxycortisol, Serum

**Clinical Information:** The adrenal glands, ovaries, testes, and placenta produce steroid hormones, which can be subdivided into 3 major groups: mineral corticoids, glucocorticoids, and sex steroids. Synthesis proceeds from cholesterol along 3 parallel pathways, corresponding to these 3 major groups of steroids, through successive side-chain cleavage and hydroxylation reactions. At various levels of each pathway, intermediate products can move into the respective adjacent pathways via additional, enzymatically catalyzed reactions (see Steroid Pathways in Special Instructions). 21-Deoxycortisol is an intermediate steroid in the glucocorticoid pathway. While the main substrate flow in glucocorticoid synthesis proceeds from 17-hydroxyprogesterone via 21-hydroxylation to 11-deoxycortisol and then, ultimately, to cortisol, a small proportion of 17-hydroxyprogesterone is also hydroxylated at carbon number 11 by 11-beta-hydroxylase 1 (CYP11B1), yielding 21-deoxycortisol. This in turn can also serve as a substrate for 21-hydroxylase (CYP21A2), resulting in formation of cortisol. The major diagnostic utility of measurements of steroid synthesis intermediates lies in the diagnosis of disorders of steroid synthesis, in particular congenital adrenal hyperplasia (CAH). All types of CAH are associated with cortisol deficiency with the exception of CYP11B2 deficiency and isolated impairments of the 17-lyase activity of CYP17A1 (this enzyme also has 17-alpha-hydroxylase activity). In case of severe illness or trauma, CAH predisposes patients to poor recovery or death. Patients with the most common form of CAH (21-hydroxylase deficiency, >90% of cases), with the third most common form of CAH (3-beta-steroid dehydrogenase deficiency, <3% of cases) and those with the extremely rare StAR (steroidogenic acute regulatory protein) or 20,22 desmolase deficiencies, might also suffer mineral corticoid deficiency, as the enzyme blocks in these disorders are proximal to potent mineral corticoids. These patients might suffer salt-wasting crises in infancy. By contrast, patients with the second most common form of CAH, 11-hydroxylase deficiency (<5% of cases), are normotensive or hypertensive, as
the block affects either CYP11B1 or CYP11B2, but rarely both, thus ensuring that at least corticosterone is still produced. In addition, patients with all forms of CAH might suffer the effects of substrate accumulation proximal to the enzyme block. In the 3 most common forms of CAH the accumulating precursors spill over into the sex steroid pathway, resulting in virilization of females or, in milder cases, in hirsutism, polycystic ovarian syndrome or infertility, as well as in possible premature adrenarche and pubarche in both genders. Measurement of the various precursors of mature mineral corticoids and glucocorticoids, in concert with the determination of sex steroid concentrations, allows diagnosis of CAH and its precise type, and serves as an aid in monitoring steroid replacement therapy and other therapeutic interventions. Measurement of 21-deoxycortisol can supplement or confirm 17-hydroxyprogesterone and androstenedione measurements in the diagnosis of difficult cases of CAH presumed to be due to CYP21A2 deficiency. 11-Hydroxylation remains intact in such patients. However, since the CYP21A2 enzyme block prevents formation of 11-deoxycortisol, while simultaneously increasing the concentrations of the precursor, 17-hydroxyprogesterone, unoccupied CYP11B1 starts to 11-hydroxylate the abundant 17-hydroxyprogesterone substrate into 21-deoxycortisol. The 21-deoxycortisol accumulates, as the diminished or absent CYP21A2 activity slows or prevents its conversion into cortisol. For other forms of CAH the following tests might be relevant: -11-Hydroxylase deficiency: - DOC / 11-Deoxycortisol, Serum - CORTC / Corticosterone, Serum - PRA / Renin Activity, Plasma - ALDS / Aldosterone, Serum -3-Beta-steroid-dehydrogenase deficiency: - 17PRN / Pregnenolone and 17-Hydroxypregnenolone -17-Hydroxylase deficiency or 17-lyase deficiency (CYP17A1 has both activities): - PREGN / Pregnenolone, Serum - 17OHP / 17-Hydroxyprogrenolone, Serum - PGSN / Progesterone, Serum - OHPG / 17-Hydroxyprogesterone, Serum - DHEA_ / Dehydroepiandrosterone (DHEA), Serum - ANST / Androstenedione, Serum Cortisol should be measured in all cases of suspected CAH. It has been suggested that in the pubertal patient with 21-hydroxylase deficiency, 21-deoxycortisol may be useful and better than 17-hydroxyprogesterone for therapeutic decisions.

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**Useful For:** As an adjunct to measurement of 17-hydroxyprogesterone, androstenedione, and cortisol in the diagnosis of difficult cases of suspected 21-hydroxylase (CYP21A2) deficiency Identifying heterozygote CYP21A2 deficiency carriers As an adjunct to measurements of 17-hydroxyprogesterone, androstenedione, testosterone, and, in females, estradiol in the follow-up of children with CYP21A2 deficiency

**Interpretation:** In untreated 21-hydroxylase (CYP21A2) deficiency, 21-deoxycortisol serum concentrations on average exceed the upper limit of the reference range 30-fold to 40-fold. 21-Hydroxyprogesterone concentrations are particularly useful in equivocal cases of suspected 21-hydroxylase deficiency. Most untreated patients with 21-hydroxylase deficiency have serum 17-hydroxyprogesterone concentrations well in excess of 1,000 ng/dL. For the few patients with levels in the range of greater than 630 ng/dL (upper limit of reference range for newborns) to 2,000 ng/dL or 3,000 ng/dL, it might be prudent to consider 11-hydroxylase deficiency as an alternative diagnosis. This is particularly true if serum androstenedione concentrations are also only mildly-to-modestly elevated, and if the phenotype is not salt wasting but either simple virilizing (female) or normal (female or male). 11-Hydroxylase deficiency, in particular if it affects 11 beta-hydroxylase 1 (CYP11B1), can be associated with modest elevations in serum 17-hydroxyprogesterone concentrations. In these cases testing for CYP11B1 deficiency and 11 beta-hydroxylase 2 (CYP11B2) deficiency should be considered and interpreted as described above. Alternatively, measurement of 21-deoxycortisol might be useful in such cases. This minor pathway metabolite accumulates in CYP21A2 deficiency, as it requires 21-hydroxylation to be converted to cortisol, but is usually not elevated in CYP11B1 deficiency, since its synthesis requires via 11-hydroxylation of 17-hydroxyprogesterone. For genetic counseling purposes, identification of asymptomatic carriers of CYP21A2 mutations and deletions is sometimes required. The gold-standard is full DNA sequencing of CYP21A2, its pseudogene CYP21A1P, and, if possible, recombinants of gene and pseudogene, along with deletion detection. Such a procedure is costly and complex, and often has a slow turnaround time. Therefore, many laboratories perform less complex, but also less complete, mutation and deletion assessments, which may miss a significant minority of heterozygote carriers. Biochemical testing using adrenocorticotropic hormone (ACTH) ACTH1-24 adrenal stimulation represents an alternative. However, for 17-hydroxyprogesterone and androstenedione measurements there is significant overlap between poststimulation results in normals and in heterozygote carriers. By contrast, poststimulation 21-deoxycortisol concentrations of 55 ng/dL identify virtually all heterozygote carriers, with minimal overlap with normal subjects. The goal of
congenital adrenal hyperplasia (CAH) treatment is normalization of cortisol levels and ideally also of sex steroid levels. Serum 17-hydroxyprogesterone, androstenedione, and testosterone should be measured and used to guide treatment modifications. Normal prepubertal androgen levels may be difficult to achieve, but if testosterone levels are within the reference range, androstenedione levels up to 100 ng/dL are usually regarded as acceptable. 17-Hydroxyprogesterone levels should not significantly exceed the normal reference range at any time of the day. However, during puberty, the changing levels of sex steroid production may make 17-hydroxyprogesterone measurements less reliable. Since 21-deoxycortisol is not a sex-steroid precursor, its levels appear more reliable during the pubertal period, again, the aim being not to exceed the reference range significantly.

**Reference Values:**

<5.0 ng/dL

Reference values apply to all ages.

**Clinical References:**


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**OH21**

**21-Hydroxylase Antibodies, Serum**

**Clinical Information:** Chronic primary adrenal insufficiency (Addison disease) is most commonly caused by the insidious autoimmune destruction of the adrenal cortex and is characterized by the presence of adrenal cortex autoantibodies in the serum. It can occur sporadically or in combination with other autoimmune endocrine diseases, that together comprise Type I or Type II autoimmune polyglandular syndrome (APS). The microsomal autoantigen 21-hydroxylase (55 kilodalton) has been shown to be the primary autoantigen associated with autoimmune Addison disease. 21-Hydroxylase antibodies are markers of autoimmune Addison disease, whether it presents alone, or as part of Type I or Type II (APS).

**Useful For:** Investigation of adrenal insufficiency Aid in the detection of those at risk of developing autoimmune adrenal failure in the future

**Interpretation:** Positive results (> or =1 U/mL) indicate the presence of adrenal autoantibodies consistent with Addison disease.

**Reference Values:**

<1 U/mL

Reference values apply to all ages.


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**CYPZ**

**21-Hydroxylase Gene (CYP21A2), Full Gene Analysis**

**Clinical Information:** Congenital adrenal hyperplasia (CAH), with an incidence rate of 1 in 10,000 to 18,000 live births, is one of the most common inherited syndromes. The condition is characterized by impaired cortisol production due to inherited defects in steroid biosynthesis. The clinical consequences of CAH, besides diminished cortisol production, depend on which enzyme is affected and whether the loss
of function is partial or complete. In greater than 90% of CAH cases, the affected enzyme is 21-steroid hydroxylase, encoded by the CYP21A2 gene located on chromosome 6 within the highly recombinant human histocompatibility complex locus. 21-hydroxylase deficient CAH is inherited in an autosomal recessive pattern and has a spectrum of clinical phenotypes depending upon residual enzyme activity. Excessive adrenal androgen biosynthesis results in varying degrees of virilization. If there is some residual enzyme activity, a non-classical phenotype results, with signs of hyperandrogenism typically starting in later childhood or adolescence. Individuals with severe enzyme deficiency have classical CAH, with prenatal onset of virilization. Classical CAH which is subdivided into simple-virilizing (minimal residual enzyme activity) and salt-wasting (no residual enzyme activity) forms. Patients with salt-wasting CAH have both cortisol and mineral corticoid deficiency and are at risk for life-threatening salt-wasting crises if untreated. Because of its high incidence rate, 21-hydroxylase deficiency is screened for in most US newborn screening programs, typically by measuring 17-hydroxyprogesterone concentrations in blood spots by immunoassay. Confirmation by other testing strategies (eg, LC-MS/MS, CAHBS / Congenital Adrenal Hyperplasia (CAH) Newborn Screening, Blood Spot), or retesting after several weeks, is required for most positive screens because of the high false-positive rates of the immunoassays (due to physiological elevations of 17-hydroxyprogesterone in premature babies and immunoassay cross-reactivity with other steroids). In a small percentage of cases, additional testing will fail to provide a definitive diagnosis. In addition, screening strategies can miss many non-classical cases, which may present later in childhood or adolescence and require more extensive steroid hormone profiling, including testing before and after adrenal stimulation with adrenocorticotropic hormone (ACTH)-1-24. For these reasons, genetic diagnosis plays an important ancillary role in both classical and non-classical cases. In addition, the high carrier frequency (approximately 1 in 50) for CYP21A2 mutations makes genetic diagnosis important for genetic counseling. Genetic testing can also play a role in prenatal diagnosis of 21-hydroxylase deficiency. However, accurate genetic diagnosis continues to be a challenge because most of the mutations arise from recombination events between CYP21A2 and its highly homologous pseudogene, CYP21A1P (transcriptionally inactive). In particular, partial or complex rearrangements (with or without accompanying gene duplication events), which lead to reciprocal exchanges between gene and pseudogene, can present severe diagnostic challenges. Comprehensive genetic testing strategies must therefore allow accurate assessment of most, or all, known rearrangements and mutations, as well as unequivocal determination of whether the observed changes are located within a potentially transcriptionally active genetic segment. Testing of additional family members is often needed for clarification of genetic test results.

**Useful For:** Carrier screening and diagnosis of 21-hydroxylase deficient congenital adrenal hyperplasia (CAH) in individuals with a personal or family history of 21-hydroxylase deficiency, or as follow-up to positive CAH newborn screens and/or measurement of basal and adrenocorticotropic hormone-1-24 stimulated 17-hydroxyprogesterone, androstenedione, and other adrenal steroid levels. May be used to identify CYP21A2 mutations in individuals with a suspected diagnosis of 21-hydroxylase deficient CAH when a common mutation panel is negative or only identifies 1 mutation. In prenatal cases of ambiguous genitalia detected by ultrasound, particularly when the fetus is confirmed XX female by chromosome analysis. This test code should also be used for known/familial variant analysis for CYP21A2. Due to the complexity of the CYP21A2 locus, site specific testing for known/familial variants is not offered for this gene.

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.


**DD22F** 35246

**22q11.2 Deletion/Duplication, FISH**

**Clinical Information:** The 22q deletion syndrome and 22q duplication syndrome have overlapping phenotypes. Deletions of 22q are associated with DiGeorge and velocardiofacial syndrome. These syndromes are manifested by the presence of growth deficiency, global developmental delay, heart defect, and hearing loss. The major birth defects include palatal clefting or insufficiency and thymus aplasia. Prominent facial features are widely spread eyes, superior placement of eyebrows, downward slanting palpebral fissures with or without ptosis (droopy upper eyelid), mild micrognathia (small jaw), and a long, narrow face. FISH studies are highly specific and do not exclude other chromosome abnormalities.

**Useful For:** Establishing a diagnosis of 22q deletion/duplication syndromes Detecting cryptic rearrangements involving 22q11.2 or 22q11.3 that are not demonstrated by conventional chromosome studies

**Interpretation:** Any individual with a normal signal pattern in each metaphase is considered negative for this probe. Any patient with a FISH signal pattern indicating loss of the critical region (1 signal) will be reported as having a deletion of the region tested by this probe. This is consistent with a diagnosis of 22q deletion syndrome. Any patient with a FISH signal pattern indicating duplication of the critical region (3 signals) will be reported as having a duplication of the region tested by this probe. This is consistent with a diagnosis 22q duplication syndrome.

**Reference Values:** An interpretive report will be provided.


**25HDN** 83670

**25-Hydroxyvitamin D2 and D3, Serum**

**Clinical Information:** Vitamin D is a generic designation for a group of fat-soluble, structurally similar sterols, which act as hormones. This test is the preferred initial test for assessing vitamin D status and most accurately reflects the body’s vitamin D stores. In the presence of renal disease, testing 1,25-dihydroxyvitamin D (DHVD) levels might be needed to adequately assess vitamin D status. DHVD testing alone may not clearly indicate deficiencies of vitamin D stores. Vitamin D compounds in the body are exogenously derived by dietary means; from plants as 25-hydroxyvitamin D2 (ergocalciferol or calciferol) or from animal products as 25-hydroxyvitamin D3 (cholecalciferol or calcidiol). Vitamin D may also be endogenously derived by conversion of 7-dihydrocholesterol to 25-hydroxyvitamin D3 in the skin upon ultraviolet exposure. 25HDN is subsequently formed by hydroxylation (CYP2R1) in the liver. 25HDN is a prohormone that represents the main reservoir and transport form of vitamin D, being stored in adipose tissue and tightly bound by a transport protein while in circulation. Biological activity is expressed in the form of DHVD, the active metabolite of 25HDN. 1-Alpha-hydroxylation (CYP27B1) occurs on demand, primarily in the kidneys, under the control of parathyroid hormone (PTH) before expressing biological activity. Like other steroid hormones, DHVD binds to a nuclear receptor, influencing gene transcription patterns in target organs. 25HDN may also be converted into the inactive metabolite 24,25-dihydroxyvitamin D (24,25D) by (CYP24A1) hydroxylation. This process, regulated by PTH, might increase DHVD synthesis at the expense of the alternative hydroxylation (CYP24A1) product...
Inactivation of 25HDN and DHVD by CYP24A1 is a crucial process that prevents overproduction of DHVD and resultant vitamin D toxicity. Based on these considerations circulating 25HDN is the best indicator of optimal vitamin D body stores. The exact levels of optimal circulating 25HDN concentrations remain a matter of debate. Mild-to-modest deficiency can be associated with osteoporosis or secondary hyperparathyroidism. Severe deficiency may lead to failure to mineralize newly formed osteoid in bone, resulting in rickets in children and osteomalacia in adults. The consequences of vitamin D deficiency on organs other than bone are not fully known, but might include increased susceptibility to infections, muscular discomfort, and an increased risk of colon, breast, and prostate cancer. Modest 25HDN deficiency is common; in institutionalized elderly, its prevalence may be greater than 50%. Although much less common, severe deficiency is not rare either. Reasons for suboptimal 25HDN levels include lack of sunshine exposure, a particular problem in Northern latitudes during winter; inadequate intake; malabsorption (eg, due to celiac disease); depressed hepatic vitamin D 25-hydroxylase activity, secondary to advanced liver disease; and enzyme-inducing drugs, in particular many antiepileptic drugs, including phenytoin, phenobarbital, and carbamazepine, which increase 25HDN metabolism.

**Useful For:** Diagnosis of vitamin D deficiency Differential diagnosis of causes of rickets and osteomalacia Monitoring vitamin D replacement therapy Diagnosis of hypervitaminosis D

**Interpretation:** Based on animal studies and large human epidemiological studies, 25-hydroxyvitamin D2 and D3 (25-OH-VitD) levels below 25 ng/mL are associated with an increased risk of secondary hyperparathyroidism, reduced bone mineral density, and fractures, particularly in the elderly. Intervention studies support this clinical cutoff, showing a reduction of fracture risk with 25-OH-VitD replacement. Levels less than 10 ng/mL may be associated with more severe abnormalities and can lead to inadequate mineralization of newly formed osteoid, resulting in rickets in children and osteomalacia in adults. In these individuals, serum calcium levels may be marginally low, and parathyroid hormone (PTH) and serum alkaline phosphatase are usually elevated. Definitive diagnosis rests on the typical radiographic findings or bone biopsy/histomorphometry. Baseline biochemical work-up of suspected cases of rickets and osteomalacia should include measurement of serum calcium, phosphorus, PTH, and 25-OH-VitD. In patients where testing is not completely consistent with the suspected diagnosis, in particular, if serum 25-OH-VitD levels are greater than 10 ng/mL, an alternative cause for impaired mineralization should be considered. Possible differential diagnosis includes: partly treated vitamin D deficiency, extremely poor calcium intake, vitamin D resistant rickets, renal failure, renal tubular mineral loss with or without renal tubular acidosis, hypophosphatemic disorders (eg, X-linked or autosomal dominant hypophosphatemic rickets), congenital hypoparathyroidism, activating calcium sensing receptor mutations, and osteopetrosis. Measurement of serum urea, creatinine, magnesium, and 1,25-dihydroxyvitamin D (DHVD) is recommended as a minimal additional workup for these patients. 25-OH-VitD replacement in the United States typically consists of vitamin D2. Lack of clinical improvement and no reduction in PTH or alkaline phosphatase may indicate patient noncompliance, malabsorption, resistance to 25-OH-VitD, or additional factors contributing to the clinical disease. Measurement of serum 25-OH-VitD levels can assist in further evaluation, in particular as the liquid chromatography-tandem mass spectrometry methodology allows separate measurement of 25-OH-VitD3 and of 25-OH-VitD2, which is derived entirely from dietary sources or supplements. Patients who present with hypercalcemia, hyperphosphatemia, and low PTH may suffer either from ectopic, unregulated conversion of 25-OH-VitD to 1,25-OH-VitD, as can occur in granulomatous diseases, particular sarcoid, or from nutritionally-induced hypervitaminosis D. Serum 1,25-OH-VitD levels will be high in both groups, but only patients with hypervitaminosis D will have serum 25-OH-VitD concentrations of greater than 80 ng/mL, typically greater than 150 ng/mL.

**Reference Values:**

<table>
<thead>
<tr>
<th>TOTAL 25-HYDROXYVITAMIN D2 AND D3 (25-OH-VitD)</th>
<th>Reference Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 ng/mL (severe deficiency)*</td>
<td></td>
</tr>
<tr>
<td>10-19 ng/mL (mild to moderate deficiency)**</td>
<td></td>
</tr>
<tr>
<td>20-50 ng/mL (optimum levels)***</td>
<td></td>
</tr>
<tr>
<td>51-80 ng/mL (increased risk of hypercalciuria)****</td>
<td></td>
</tr>
<tr>
<td>&gt;80 ng/mL (toxicity possible)******</td>
<td></td>
</tr>
</tbody>
</table>

*Could be associated with osteomalacia or rickets

**May be associated with increased risk of osteoporosis or secondary hyperparathyroidism

***Optimum levels in the healthy population; patients with bone disease may benefit from higher concentrations.
levels within this range

****Sustained levels >50 ng/mL 25OH-VitD along with prolonged calcium supplementation may lead to hypercalciuria and decreased renal function

******80 ng/mL is the lowest reported level associated with toxicity in patients without primary hyperparathyroidism who have normal renal function. Most patients with toxicity have levels >150 ng/mL. Patients with renal failure can have very high 25-OH-VitD levels without any signs of toxicity, as renal conversion to the active hormone 1,25-OH-VitD is impaired or absent.

These reference ranges represent clinical decision values, based on the 2011 Institute of Medicine report, that apply to males and females of all ages, rather than population-based reference values. Population reference ranges for 25-OH-VitD vary widely depending on ethnic background, age, geographic location of the studied populations, and the sampling season. Population-based ranges correlate poorly with serum 25-OH-VitD concentrations that are associated with biologically and clinically relevant vitamin D effects and are therefore of limited clinical value.

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.


25-Hydroxyvitamin D:24,25-Dihydroxyvitamin D Ratio, Serum

Clinical Information: Vitamin D is a generic designation for a group of fat-soluble, structurally similar sterols. The 25HDN / 25-Hydroxyvitamin D2 and D3, Serum assay is the preferred initial test for assessing vitamin D status and most accurately reflects the body's vitamin D stores. In the presence of renal disease, DHVD / 1,25-Dihydroxyvitamin D, Serum testing might be needed to adequately assess vitamin D status. For patients with loss of function inactivating CYP24A1 mutations, this test (2425D / 25-Hydroxyvitamin D2 and D3:24,25-Dihydroxyvitamin D Ratio, Serum) may be helpful Loss of function mutations in the CYP24A1 gene have been shown to lead to insufficient deactivation of bioactive vitamin D metabolites, resulting in a phenotype characterized by suppressed serum parathyroid hormone (PTH), increased serum 1,25-dihydroxyvitamin D (DHVD) concentrations, hypercalcemia, and hypercalciuria or nephrolithiasis. Vitamin D compounds in the body are exogenously derived by dietary means; from plants as 25-hydroxyvitamin D2 (ergocalciferol or calciferol) or from animal products as 25-hydroxyvitamin D3 (cholecalciferol or calcidiol). Vitamin D may also be endogenously derived by conversion of 7-dihydrocholesterol to 25-hydroxyvitamin D3 in the skin upon ultraviolet exposure. 25-Hydroxyvitamin D (25HDN) is subsequently formed by hydroxylation (CYP2R1) in the liver. 25HDN is a prohormone that represents the main reservoir and transport form of vitamin D, being stored in adipose tissue and tightly bound by a transport protein while in circulation. Biological activity is expressed in the form of DHVD the active metabolite of 25HDN. 1-Alfa-hydroxylation (CYP27B1) occurs on demand, primarily in the kidneys, under the control of parathyroid hormone (PTH) before expressing biological activity. Like other steroid hormones, DHVD binds to a nuclear receptor, influencing gene transcription patterns in target organs. 25HDN may also be converted into the inactive metabolite 24,25-dihydroxyvitamin D (24,25D) by (CYP24A1) hydroxylation. This process regulated by parathyroid hormone (PTH) might increase DHVD synthesis at the expense of the alternative hydroxylation (CYP24A1) product 24,25D. Inactivation of 25HDN and DHVD by CYP24A1 is a crucial process that prevents over production of DHVD and resultant vitamin D toxicity. DHVD stimulates
calcium absorption in the intestine and its production is tightly regulated through concentrations of serum calcium, phosphorus, and PTH. DHVD promotes intestinal calcium absorption and, in concert with PTH, skeletal calcium deposition, or less commonly, calcium mobilization. Renal calcium and phosphate reabsorption are also promoted, while prepro-PTH mRNA expression in the PTH glands is downregulated. The net result is a positive calcium balance, increasing serum calcium and phosphate levels, and falling PTH concentrations. In addition to its effects on calcium and bone metabolism, DHVD regulates the expression of a multitude of genes in many other tissues including immune cells, muscle, vasculature, and reproductive organs. DHVD levels are decreased in hypoparathyroidism and in chronic renal failure. DVHD levels may be high in primary hyperparathyroidism and in physiologic hyperparathyroidism secondary to low calcium or vitamin D intake. Some patients with granulomatous diseases (eg, sarcoidosis) and malignancies containing nonregulated 1-alpha hydroxylase in the lesion might have hypercalcemia that appears vitamin D mediated with normal or high serum phosphate (hyperphosphatemia) and hypercalcemia (both of which might be severe), in addition to low parathyroid hormone (PTH) and absent parathyroid hormone-related peptide (PTHRP). Differential diagnostic considerations include vitamin D intoxication and CYP24A1 deficiency.

**Useful For:** As a screening test for inactivating CYP24A1 mutations in patients with symptoms, signs, or biochemical findings of parathyroid hormone (PTH)-independent hypercalcemia or hypercalciuria.

**Interpretation:** Results should be interpreted in the context of other biochemical findings including serum calcium, parathyroid hormone (PTH), and 1,25 dihydroxyvitamin D (DHVD) concentrations. If 25-hydroxyvitamin D (25HDN) result is less than 20 ng/mL, the ratio of 25-OH-D to 24,25-dihydroxyvitamin D (24,25D) will be falsely elevated since there is no inactivation of 25-OH-D to 24,25D. 24,25D formation by CYP24A1 is dependent on CYP24A1 activity and the concentrations of its substrate, 25HDN. The ratio of 25HDN to 24,25D, therefore, allows the most reliable estimation of CYP24A1 activity. Ratios of 25HDN to 24,25D less than 25 may be interpreted as normal, though ratio of less than 25 may also be observed in heterozygous carriers of CYP24A1 mutations. Ratios of 25HDN to 24,25D between the 25 and 80 range may be seen in patients with low vitamin D or heterozygous CYP24A1 mutations. Confirmation with molecular testing is recommended. Confirmation with molecular testing is also recommended for ratios of 25HDN to 24,25D greater than 80, as this may indicate a probable biallelic CYP24A1 mutation or deletion.

**Reference Values:**
Interpretative commentary provided based on 25-hydroxyvitamin D (25HDN) to 24,25-dihydroxyvitamin D (24,25D) ratio result.

- 25HDN to 24,25D ratio less than 25*
  *Interpretation: Normal (Ratio of less than 25 may also be observed in heterozygous carriers of CYP24A1 mutations)

- 25HDN to 24,25D ratio between 25-80**
  **Interpretation: Ratios in the 25 to 80 range can be seen in patients with low vitamin D or heterozygous CYP24A1 mutations. Confirmation with molecular testing is recommended.

- 25HDN to 24,25D ratio greater than 80***
  ***Interpretation: Ratios greater than 80 indicate probable biallelic CYP24A1 mutation or deletion. Confirmation with molecular testing is recommended.

Reference values not applicable for 24,25 Dihydroxyvitamin D Total result.

Results should be interpreted in the context of other biochemical findings including serum calcium, parathyroid hormone, and 1,25 dihydroxyvitamin D concentrations. If 25-OH-D is less than 20 ng/ml the ratio of 25-OH-D to 24,25-dihydroxyvitamin D will be falsely elevated since there is no inactivation 25-OH-D to 24,25-dihydroxyvitamin D.

F5NUL 5'Nucleotidase

Useful For:

Reference Values:
0 - 15 U/L

MTHAC 5,10-Methylenetetrahydrofolate Reductase A1298C, Mutation, Blood

Clinical Information: Hyperhomocysteinemia is an independent risk factor for coronary artery disease, acute myocardial infarction, peripheral arterial disease, stroke, and venous thromboembolism. Homocysteine is a sulfhydryl-containing amino acid formed as an intermediary during the conversion of methionine to cystathionine. Genetic or nutrition-related disturbances (e.g., deficiency of vitamins B12, B6, and folic acid) may impair the transsulfuration or remethylation pathways of homocysteine metabolism and cause hyperhomocysteinemia. The enzyme MTHFR catalyzes reduction of 5,10-methylene tetrahydrofolate to 5-methyl tetrahydrofolate, the major form of folate in plasma; 5-methyl tetrahydrofolate serves as a methyl donor for remethylation of homocysteine to methionine. Patients with severe MTHFR deficiency (enzymatic activity 0%-20% of normal) develop homocysteinuria, a severe disorder with a wide range of associated clinical manifestations, including developmental delay, mental retardation, and premature vascular disease. Seven unique MTHFR mutations have been associated with homocysteinuria, all among patients who were either homozygous or compound heterozygotes for one or more of these mutations. A milder deficiency of MTHFR, with approximately 50% residual enzyme activity and marked enzyme lability to heat inactivation, is associated with a cytosine to thymine mutation at nucleotide position 677 (C677->T), encoding for an alanine-223 to valine substitution (MTHFR C677T). A second mutation in MTHFR exon 7, A1298C, results in a conversion of a glutamic acid codon to an alanine codon. The MTHFR A1298C reduces MTHFR activity to a lesser extent than C677T, but compound heterozygous A1298C/C677T may develop hyperhomocysteinemia. For suspected hyperhomocysteinemia, we recommend that a basal plasma homocysteine level be measured. Vitamin B12, B6, and folic acid levels should be measured in patients with hyperhomocysteinemia.

Useful For: Direct mutation analysis for the MTHFR A1298C mutation should be reserved for patients with coronary artery disease, acute myocardial infarction, peripheral vascular artery disease, stroke, or venous thromboembolism, who have increased basal homocysteine levels or an abnormal methionine-load test.

Interpretation: The interpretive report will include specimen information, assay information, background information, and conclusions based on the test results (negative, heterozygous MTHFR A1298C, homozygous MTHFR A1298C).

Reference Values:
Negative

5,10-Methylenetetrahydrofolate Reductase C677T and A1298C Mutations, Blood

**Clinical Information:** Hyperhomocysteinemia is an independent risk factor for coronary artery disease, acute myocardial infarction, peripheral arterial disease, stroke, and venous thromboembolism. Homocysteine is a sulfhydryl-containing amino acid formed as an intermediary during the conversion of methionine to cystathionine. Genetic or nutrition-related disturbances (eg, deficiency of vitamins B12, B6, and folic acid) may impair the transsulfuration or remethylation pathways of homocysteine metabolism and cause hyperhomocysteinemia. The enzyme MTHFR catalyzes reduction of 5,10-methylene tetrahydrofolate to 5-methyl tetrahydrofolate, the major form of folate in plasma; 5-methyl tetrahydrofolate serves as a methyl donor for remethylation of homocysteine to methionine. Patients with severe MTHFR deficiency (enzymatic activity 0%-20% of normal) develop homocysteinuria, a severe disorder with a wide range of associated clinical manifestations, including developmental delay, mental retardation, and premature vascular disease. Seven unique MTHFR mutations have been associated with homocysteinuria, all among patients who were either homozygous or compound heterozygotes for 1 or more of these mutations. A milder deficiency of MTHFR, with approximately 50% residual enzyme activity and marked enzyme lability to heat inactivation, is associated with a cytosine to thymine mutation at nucleotide position 677, encoding for an alanine-223 to valine substitution (MTHFR C677T). A second mutation in MTHFR exon 7, A1298C, results in a conversion of a glutamic acid codon to an alanine codon. The MTHFR A1298C mutation reduces MTHFR activity to a lesser extent than C677T, but compound heterozygous MTHFR A1298C/C677T may develop hyperhomocysteinemia. For suspected hyperhomocysteinemia, we recommend that a basal plasma homocysteine level be measured. Vitamin B12, B6, and folic acid levels should be measured in patients with hyperhomocysteinemia.

**Useful For:** Direct mutation analysis for the MTHFR C677T and/or A1298C mutations should be reserved for patients with coronary artery disease, acute myocardial infarction, peripheral vascular artery disease, stroke, or venous thromboembolism who have increased basal homocysteine levels or an abnormal methionine-load test.

**Interpretation:** The interpretive report will include specimen information, assay information, background information, and conclusions based on the test results (negative, heterozygous MTHFR C677T, homozygous MTHFR C677T; negative, heterozygous MTHFR A1298C, homozygous MTHFR A1298C).

**Reference Values:**
Negative

**Clinical References:**
disease, acute myocardial infarction, peripheral arterial disease, stroke, and venous thromboembolism. Homocysteine is a sulfhydryl-containing amino acid formed as an intermediary during the conversion of methionine to cystathionine. Genetic or nutrition-related disturbances (eg, deficiency of vitamins B12, B6, and folic acid) may impair the transsulfuration or remethylation pathways of homocysteine metabolism and cause hyperhomocysteinemia. The enzyme MTHFR catalyzes reduction of 5,10-methylene tetrahydrofolate to 5-methyl tetrahydrofolate, the major form of folate in plasma; 5-methyl tetrahydrofolate serves as a methyl donor for remethylation of homocysteine to methionine. Patients with severe MTHFR deficiency (enzymatic activity 0%-20% of normal) develop homocysteinuria, a severe disorder with a wide range of associated clinical manifestations, including developmental delay, mental retardation, and premature vascular disease. Seven unique MTHFR mutations have been associated with homocysteinuria, all among patients who were either homozygous or compound heterozygotes for 1 or more of these mutations. A milder deficiency of MTHFR, with approximately 50% residual enzyme activity and marked enzyme liability to heat inactivation, is associated with a cytosine to thymine mutation at nucleotide position 677 (C677->T), encoding for an alanine-223 to valine substitution (MTHFR C677T). Patients who are homozygous for the MTHFR C677T mutation may develop hyperhomocysteinemia, especially with concurrent deficiency of vitamins B12, B6 (pyridoxine), or folic acid. This mutation is quite common, with a carrier frequency of 31% to 39% (homozygote frequency 9%-17%) among the white North American population. The MTHFR C677T mutation test is a direct assay of patient leukocyte genomic DNA. For suspected hyperhomocysteinemia, we recommend that a basal plasma homocysteine level be measured. Vitamin B12, B6, and folic acid levels should be measured in patients with hyperhomocysteinemia.

**Useful For:** Direct mutation analysis for the MTHFR C677T mutation should be reserved for patients with coronary artery disease, acute myocardial infarction, peripheral vascular artery disease, stroke, or venous thromboembolism who have increased basal homocysteine levels or an abnormal methionine-load test.

**Interpretation:** The interpretive report will include specimen information, assay information, background information, and conclusions based on the test results (negative, heterozygous MTHFR C677T, homozygous MTHFR C677T).

**Reference Values:**


**5-Flucytosine, Serum**

**Clinical Information:** Flucytosine is a broad-spectrum antifungal agent generally used in combined therapy (often with amphotericin B) for treatment of fungal infections such as cryptococcal meningitis. Concerns with toxicity (bone marrow suppression, hepatic dysfunction) and development of fungal resistance limit the use of flucytosine, particularly as a monotherapy. The drug is well-absorbed orally, but can also be administered intravenously (available outside of the United States). There is good correlation between serum concentrations of flucytosine with both efficacy and risk for toxicity. Because of the drug's short half-life (3-6 hours), therapeutic monitoring is typically performed at peak levels, 1 to 2 hours after an oral dose or 30 minutes after an intravenous administration. Flucytosine is eliminated primarily as unmetabolized drug in urine. Patients with renal dysfunction may require dose adjustments or more frequent monitoring to ensure that serum concentrations do not accumulate to excessive levels.

**Clinical Information:** Flucytosine is a broad-spectrum antifungal agent generally used in combined therapy (often with amphotericin B) for treatment of fungal infections such as cryptococcal meningitis. Concerns with toxicity (bone marrow suppression, hepatic dysfunction) and development of fungal resistance limit the use of flucytosine, particularly as a monotherapy. The drug is well-absorbed orally, but can also be administered intravenously (available outside of the United States). There is good correlation between serum concentrations of flucytosine with both efficacy and risk for toxicity. Because of the drug's short half-life (3-6 hours), therapeutic monitoring is typically performed at peak levels, 1 to 2 hours after an oral dose or 30 minutes after an intravenous administration. Flucytosine is eliminated primarily as unmetabolized drug in urine. Patients with renal dysfunction may require dose adjustments or more frequent monitoring to ensure that serum concentrations do not accumulate to excessive levels.
Nephrotoxicity associated with use of amphotericin B can affect elimination of flucytosine when the drugs are coadministered.

**Useful For:** Monitoring serum concentration during therapy Evaluating potential toxicity May be useful to evaluate patient compliance

**Interpretation:** Most individuals display optimal response to flucytosine when peak serum levels (1-2 hours after oral dosing) are greater than 25.0 mcg/mL. Some infections may require higher concentrations for efficacy. Toxicity is more likely when peak serum concentrations are greater than 100.0 mcg/mL

**Reference Values:**
Therapeutic concentration: Peak >25.0 mcg/mL (difficult infections may require higher concentrations)
Toxic concentration: Peak >100.0 mcg/mL


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**F5HAR**

### 5-HIAA (5-Hydroxyindoleacetic Acid), Random Urine

**Reference Values:**

<table>
<thead>
<tr>
<th>5-HIAA (mg/g creat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-10 YRS: 12.0 or less</td>
</tr>
<tr>
<td>&gt;10 YRS: 10.0 or less</td>
</tr>
</tbody>
</table>

<p>| Creatinine, Random Urine (mg/dL) |</p>
<table>
<thead>
<tr>
<th>Age</th>
<th>mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 Months</td>
<td>2-32</td>
</tr>
<tr>
<td>7-11 Months</td>
<td>2-36</td>
</tr>
<tr>
<td>1-2 Years</td>
<td>2-128</td>
</tr>
<tr>
<td>3-8 Years</td>
<td>2-149</td>
</tr>
<tr>
<td>9-12 Years</td>
<td>2-183</td>
</tr>
<tr>
<td>&gt;12 Years</td>
<td></td>
</tr>
<tr>
<td>Males:</td>
<td>20-370</td>
</tr>
<tr>
<td>Females:</td>
<td>20-320</td>
</tr>
</tbody>
</table>

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**HIAA**

### 5-Hydroxyindoleacetic Acid (5-HIAA), 24 Hour, Urine

**Clinical Information:** 5-Hydroxyindoleacetic acid (5-HIAA) is the major metabolite of serotonin and is excreted in the urine. Intestinal carcinoid tumors along with neuroendocrine tumors can produce excess amounts of 5-HIAA and serotonin especially in individuals with carcinoid syndrome. Carcinoid syndrome is characterized by carcinoid tumors, flushing, heart disease, and hepatomegaly. Measurement of 5-HIAA in a 24-hour urine specimen can diagnose carcinoid disease with a high specificity.

**Useful For:** Biochemical diagnosis and monitoring of intestinal carcinoid syndrome

**Interpretation:** Elevated excretion of 5-hydroxyindoleacetic acid is a probable indicator of the presence of a serotonin-producing tumor, if pharmacological and dietary artifacts have been ruled out.

**Reference Values:**

< or =8 mg/24 hours
For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.


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**F5M 57101**

**5-Methyltetrahydrofolate**

**Clinical Information:** CSF 5-Methyltetrahydrofolate (NC01) is useful for determining a deficiency of folate in the central nervous system. CSF 5-Methyltetrahydrofolate (NC01) may also be used for assessment of Variants of Uncertain Significance (VUS) identified during genetic testing (e.g. Next Generation Sequencing or Capillary Sequencing Testing). CLINICAL 5-Methyltetrahydrofolate (5-MTHF) is the predominant form of folate in cerebrospinal fluid (CSF). Low CSF 5-MTHF levels are associated with inborn errors of metabolism affecting folate metabolism, dietary deficiency of folate, cerebral folate syndromes and Kearns-Sayre syndrome. Symptoms may include, anemia, developmental delay, seizures, depression and dementia.

**Reference Values:**

<table>
<thead>
<tr>
<th>5-Methyltetrahydrofolate</th>
<th>5MTHF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td><strong>(nmol/L)</strong></td>
</tr>
<tr>
<td>0-0.2</td>
<td>40-240</td>
</tr>
<tr>
<td>0.2-0.5</td>
<td>40-240</td>
</tr>
<tr>
<td>0.5-2.0</td>
<td>40-187</td>
</tr>
<tr>
<td>2.0-5.0</td>
<td>40-150</td>
</tr>
<tr>
<td>5.0-10</td>
<td>40-128</td>
</tr>
<tr>
<td>10-15</td>
<td>40-120</td>
</tr>
<tr>
<td>Adults</td>
<td>40-120</td>
</tr>
</tbody>
</table>

Note: If test results are inconsistent with the clinical presentation, please call our laboratory to discuss the case and/or submit a second sample for confirmatory testing.

**DISCLAIMER** required by the FDA for high complexity clinical laboratories: HPLC testing was developed and its performance characteristics determined by Medical Neurogenetics. These HPLC tests have not been cleared or approved by the U.S. FDA.

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**MAMMX 62732**

**6-Monoacetylmorphine (6-MAM) Confirmation, Chain of Custody, Meconium**

**Clinical Information:** Heroin (diacetylmorphine) is a semisynthetic opiate that is closely related to morphine. It is no longer used clinically in the United States, though it is used elsewhere for rapid relief of pain.(1) Like morphine and other opiates, its relaxing and euphoric qualities make heroin a popular drug of abuse. Heroin is commonly injected intravenously, although it can be administered by other means such as snorting, smoking, or inhaling vapors. Heroin shares the core structure of morphine, with the addition of 2 acetyl groups, which are thought to enhance its permeation into the central nervous system.(2,3) Heroin is metabolized by sequential removal of these acetyl groups; loss of the first acetyl
converts heroin into 6-monoacetylmorphine (6-MAM).(2,3) Heroin is rarely found in meconium since only 0.1% of a dose is excreted unchanged. 6-MAM is a unique metabolite of heroin, and its presence is a definitive indication of heroin use. Like heroin, 6-MAM has a very short half-life; however, its detection time in meconium, the first fecal material passed by the neonate, is uncharacterized. 6-MAM is further metabolized into morphine, the dominant metabolite of heroin, and morphine will typically be found in a specimen containing 6-MAM. Opiates, including heroin, have been shown to readily cross the placenta and distribute widely into many fetal tissues.(4) Opiate use by the mother during pregnancy increased the risk of prematurity and being small for gestational age. Furthermore, heroin-exposed infants exhibit an early onset of withdrawal symptoms compared with methadone-exposed infants. Heroin-exposed infants demonstrate a variety of symptoms including irritability, hypertonia, wakefulness, diarrhea, yawning, sneezing, increased hiccups, excessive sucking, and seizures. Long-term intrauterine drug exposure may lead to abnormal neurocognitive and behavioral development as well as an increased risk of sudden infant death syndrome.(5) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid.(6) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation.(7) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(6) Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection of in utero drug exposure up to 5 months before birth. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain-of-custody ensures that the test results are appropriate for legal proceedings.

**Interpretation:** The presence of 6-monoacetylmorphine (6-MAM) in meconium is definitive for heroin use by the mother. However, the absence of 6-MAM does not rule-out heroin use, because of its short half-life.

**Reference Values:**

**Negative**
- Positives are reported with a quantitative LC-MS/MS result.
- Cutoff concentration:
  - 6-MAM by LC-MS/MS: 5 ng/g

**Clinical References:**
drug of abuse. Heroin is commonly injected intravenously, although it can be administered by other means such as snorting, smoking, or inhaling vapors. Heroin shares the core structure of morphine, with the addition of 2 acetyl groups, which are thought to enhance its permeation into the central nervous system.(2,3) Heroin is metabolized by sequential removal of these acetyl groups; loss of first acetyl group converts heroin into 6-monoacetylmorphine (6-MAM) and loss of the second acetyl group converts 6-MAM to morphine, the dominant metabolite of heroin.(2,3) Heroin is rarely found intact in urine, since only 0.1% of a dose is excreted unchanged. 6-MAM is a unique metabolite of heroin, and its presence is a definitive indication of recent heroin use. Like heroin, 6-MAM has a very short half-life and detection window.

Useful For: Determination of heroin use

Interpretation: The presence of 6-monoacetylmorphine (6-MAM) in urine is definitive for recent heroin use. However, the absence of 6-MAM does not rule-out heroin use because of its short half-life. 6-MAM is typically only detectable within 24 hours of heroin use. 6-MAM is further metabolized into morphine, which may be detected 1 to 2 days after 6-MAM is no longer measurable. Morphine will typically be found in a specimen containing 6-MAM.(2,3)

Reference Values:
Negative
Cutoff concentrations:
6-MAM<br>&lt;5 ng/mL


6-Monoacetylmorphine (6-MAM), Chain of Custody, Urine

Clinical Information: Heroin (diacetylmorphine) is a semisynthetic opiate that is closely related to morphine. It is no longer used clinically in the United States, though elsewhere it is used for rapid relief of pain.(1) Like morphine and other opiates, its relaxing and euphoric qualities make heroin a popular drug of abuse. Heroin is commonly injected intravenously, although it can be administered by other means such as snorting, smoking, or inhaling vapors. Heroin shares the core structure of morphine, with the addition of 2 acetyl groups, which are thought to enhance its permeation into the central nervous system.(2,3) Heroin is metabolized by sequential removal of these acetyl groups; loss of first acetyl group converts heroin into 6-monoacetylmorphine (6-MAM) and loss of the second acetyl group converts 6-MAM to morphine, the dominant metabolite of heroin.(2,3) Heroin is rarely found intact in urine, since only 0.1% of a dose is excreted unchanged. 6-MAM is a unique metabolite of heroin, and its presence is a definitive indication of recent heroin use. Like heroin, 6-MAM has a very short half-life and detection window. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Determination of heroin use Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: The presence of 6-monoacetylmorphine (6-MAM) in urine is definitive for recent heroin use. However, the absence of 6-MAM does not rule out heroin use because of its short half-life. 6-MAM is typically only detectable within 24 hours of heroin use. 6-MAM is further metabolized into morphine, which may be detected 1 to 2 days after 6-MAM is no longer measurable. Morphine will typically be found in a specimen containing 6-MAM.(2,3)
Reference Values:
Negative
Cutoff concentrations:
6-MAM
<5 ng/mL


6-Monoacetylmorphine (6-MAM), Confirmation, Meconium

Clinical Information: Heroin (diacetylmorphine) is a semisynthetic opiate that is closely related to morphine. It is no longer used clinically in the United States, though it is used elsewhere for rapid relief of pain.(1) Like morphine and other opiates, its relaxing and euphoric qualities make heroin a popular drug of abuse. Heroin is commonly injected intravenously, although it can be administered by other means such as snorting, smoking, or inhaling vapors. Heroin shares the core structure of morphine, with the addition of 2 acetyl groups, which are thought to enhance its permeation into the central nervous system.(2,3) Heroin is metabolized by sequential removal of these acetyl groups; loss of the first acetyl converts heroin into 6-monoacetylmorphine (6-MAM).(2,3) Heroin is rarely found in meconium since only 0.1% of a dose is excreted unchanged. 6-MAM is a unique metabolite of heroin, and its presence is a definitive indication of heroin use. Like heroin, 6-MAM has a very short half-life; however, its detection time in meconium, the first fecal material passed by the neonate, is uncharacterized. 6-MAM is further metabolized into morphine, the dominant metabolite of heroin, and morphine will typically be found in a specimen containing 6-MAM. Opiates, including heroin, have been shown to readily cross the placenta and distribute widely into many fetal tissues.(4) Opiate use by the mother during pregnancy increased the risk of prematurity and being small for gestational age. Furthermore, heroin-exposed infants exhibit an early onset of withdrawal symptoms compared with methadone-exposed infants. Heroin-exposed infants demonstrate a variety of symptoms including irritability, hypertonia, wakefulness, diarrhea, yawning, sneezing, increased hiccups, excessive sucking, and seizures. Long-term intrauterine drug exposure may lead to abnormal neurocognitive and behavioral development as well as an increased risk of sudden infant death syndrome.(5) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid.(6) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation.(7) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(6)

Useful For: Detection of in utero drug exposure up to 5 months before birth

Interpretation: The presence of 6-monoacetylmorphine (6-MAM) in meconium is definitive for heroin use by the mother. However, the absence of 6-MAM does not rule-out heroin use, because of its short half-life.

Reference Values:
Negative
Positives are reported with a quantitative LC-MS/MS result.
Cutoff concentration:
6-MAM by LC-MS/MS: 5 ng/g

3. Goodman and Gilman’s. The

**68kD (hsp-70)**

**Interpretation:** Antibodies to inner ear antigen (68kD) occur in approximately 70% of patients with autoimmune hearing loss. The antibody tests to this 68kD antigen parallel with disease activity. In addition, a majority of patients positive for antibodies to 68kD are responsive to corticosteroid treatment. (Hirose et al: The Laryngoscope 109:1769 – 1999)

**Reference Values:**
Qualitative test â€“ Positive or Negative

**7AC4, Bile Acid Synthesis, Serum**

**Clinical Information:** Bile acids are synthesized from cholesterol in the liver and released into the digestive tract where they function to emulsify dietary fats and facilitate lipid absorption in the small intestine. More than 95% of bile acids are then reabsorbed primarily by active uptake in the distal ileum, while less than 5% are excreted in stool. The synthesis of bile acids in the liver is regulated by a negative feedback mechanism from the bile acids reabsorbed from the intestine. Alpha-hydroxy-4-cholesten-3-one (7aC4) is an intermediate in the biosynthesis pathway of cholesterol to bile acids. The concentration of 7aC4 in serum is a surrogate for the amount of bile acid synthesis in the liver. There is some diurnal variation in 7aC4 serum concentrations, so measurement should be performed on a fasting morning sample. Patients with increased bile acid in their stool suffer from chronic diarrhea termed bile acid diarrhea (BAD). Approximately 10% to 33% of patients with irritable bowel syndrome with primarily diarrhea (IBS-D) have BAD. Identifying patients with BAD can be done by measuring total and fractionated bile acids in stool. The increased bile acids in feces can be caused by an inability to reabsorb bile acids in the terminal ileum (bile acid malabsorption). The loss of intestinal reabsorption leads to increased synthesis of bile acids in the liver. Recent studies have shown that serum concentrations of 7aC4 are elevated in patients with BAD and can be used as a surrogate to the timed fecal collection. Several intestinal diseases or functional abnormalities can lead to BAD. Identification of these patients can influence treatment decisions that could include the use of bile acid sequestrants. Conversely, patients with IBS with predominately constipation (IBS-C) may have lower circulating 7aC4 as compared to healthy individuals.

**Useful For:** Screening for bile acid malabsorption in patients with irritable bowel syndrome-diarrhea (IBS-D)

**Interpretation:** In patients with irritable bowel syndrome-diarrhea (IBS-D), elevated 7alpha-hydroxy-4-cholesten-3-one (7AC4) is consistent with bile acid diarrhea (BAD). A result of 17.6 ng/mL or greater is 83% sensitive and 53% specific for BAD. In these cases, a confirmatory 48-hour fecal bile acid test could be considered. A result above 52.5 ng/mL is 40% sensitive and 85% specific for BAD. Interpretation in patients with chronic diarrhea:

<table>
<thead>
<tr>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 17.6</td>
<td>BAM unlikely</td>
</tr>
<tr>
<td>17.6-52.5</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>&gt; 52.5</td>
<td>BAM likely</td>
</tr>
</tbody>
</table>

**Reference Values:**
> or =18 years: 2.5-63.2 ng/mL
Reference values have not been established for patients who are <18 years of age.

A1R 113437

A1 Antigen Subtype

Clinical Information: The presence or absence of a cellular antigen is an inherited trait. As a general rule, individuals will not make antibody directed against an antigen present on their own red blood cells.

Useful For: Additional proof of alloantibody specificity Assessment of solid organ transplantation donor compatibility This test is not useful for the purpose of establishing paternity.

Interpretation: A1 antigen type will be resulted as "pos" indicating that the antigen is present, or by "neg" indicating that the antigen is absent.

Reference Values: Reported as Negative or Positive


ABONR 113498

ABO/Rh Newborn, RBC

Clinical Information: The ABO and Rh typing indicates the presence of 2 of the various blood group systems. The identification of antigens in the ABO and Rh system has its major application in the selection of blood and blood products of the appropriate ABO/Rh type for transfusion therapy and in the determination of the mother's candidacy for Rh immune globulin therapy. Weak D testing will be performed on all Rh-negative babies.

Useful For: Selecting compatible blood products for transfusion therapy Determining the need for Rh immune globulin in mother of baby

Interpretation: Agglutination of red cells with an antiserum represents the presence of the corresponding antigen on the red cells.

Reference Values: ABO and Rh blood group antigens identified


ABOMR 113490

ABORh, RBC

Clinical Information: This ABO and Rh blood typing test identifies the presence of specific red cell antigens and antibodies to determine the ABO/Rh type.
**Useful For:** Determining blood group ABO and Rh only

**Interpretation:** Standard ABO/Rh type will be reported. Routine types include: O pos, O neg, A pos, A neg, B pos, B neg, AB pos and AB neg. Any relevant discrepancies will be noted.

**Reference Values:**
ABORh: ABO and Rh blood group antigens identified


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**ACAC 82757**

**Acacia, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


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**ACARP 64717**

**Acanthamoeba species Molecular Detection, PCR, Ocular**
**Clinical Information:** Acanthamoeba are ubiquitous, free-living, microscopic amebae that cause rare, but severe, infections of the eye, skin, lungs, and central nervous system (CNS). They are found worldwide in water and soil and may enter the body through inhalation, contamination of wounds, and contact lens use. As many as 24 species comprising 18 genotypes (T1-T18) have been described, although most human infections are due to genotype T4. Given their widespread distribution in the environment, many people will be exposed to Acanthamoeba during their lifetime, but very few will become sick from this exposure. The most common form of Acanthamoeba infection is amebic keratitis (AK). Infection occurs primarily in contact lens wearers due to contamination of lenses, cleaning solutions, or storage cases. Amebae can also enter the cornea following trauma. AK is a painful, subacute corneal infection associated with extensive scarring and blindness if untreated. Cases generally respond to treatment but relapse is common. Compared to corneal infection, involvement of the CNS is rare and seen primarily in severely immunocompromised individuals such as organ transplant recipients and patients with AIDS. CNS infection may also be caused by a related ameba, Balamuthia mandrillaris. AK is usually clinically suspected based on symptoms and confocal ophthalmologic examination. Confirmation of infection is classically identified by microscopic examination and culture of corneal tissue and contact lenses or equipment using tap water agar plate overlain with bacteria as a food source for the amebae. Unfortunately, it must be held and examined for 7 days for maximum sensitivity. PCR provides a more rapid result with similar sensitivity to culture and is, therefore, the preferred method for confirming the clinical diagnosis of AK.

**Useful For:** Aids in the diagnosis of amebic keratitis in conjunction with clinical findings

**Interpretation:** A positive result indicates the presence of Acanthamoeba species DNA and is consistent with active or recent infection. While positive results are highly specific indicators of disease, they should be correlated with symptoms, clinical findings, and confocal ophthalmologic examination.

**Reference Values:**

Negative

**Clinical References:**

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**ACAR 82850**

**Acarus siro, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
Reference Values:
Class IgE kU/L  Interpretation
0            Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive
Reference values apply to all ages.


FACET 57707
Acetaminophen (Tylenol, Datril), Urine
Reference Values:
Units:    ug/mL
Note: Analysis performed on urine.
Reference ranges have not been established for urine specimens.

ACMA 37030
Acetaminophen, Serum
Clinical Information: Acetaminophen (found in Anacin-3, Comtrex, Contac, Datril, Dristan, Excedrin, Nyquil, Sinutab, Tempera, TYLENOL, Vanquish, and many others) is an analgesic, antipyretic drug lacking significant anti-inflammatory activity. It is metabolized by the liver with a normal elimination half-life of less than 4 hours. In normal therapeutic doses, a minor metabolite, possessing electrophilic alkylation activity, readily reacts with glutathione in the liver to yield a detoxified product. In overdose situations, liver glutathione is consumed and the toxic metabolite (postulated metabolite: benzoquinone) reacts with cellular proteins resulting in hepatotoxicity, characterized by centrilobular necrosis and possible death if untreated. N-acetylcysteine can substitute for glutathione and serves as an antidote. Serum concentration and half-life are the only way to assess degree of intoxication in early stages since other liver function studies (eg, bilirubin, liver function enzymes) will not show clinically significant increases until after tissue damage has occurred, at which point therapy is ineffective.

Useful For: Monitoring toxicity in overdose cases

Interpretation: The normal half-life is less than 4 hours, while the toxic half-life is greater than 4 hours. The toxic level is dependent on half-life. When the half-life is 4 hours, hepatotoxicity generally will not occur unless the concentration is above 150 mcg/mL. The level at which toxicity occurs decreases with increasing half-life until it is encountered at values as low as 50 mcg/mL when the half-life reaches 12 hours. For half-life determination, draw 2 specimens at least 4 hours apart and note the exact time of each draw. Half-life can be calculated from the concentrations and the time interval.


FACTO 90247
Acetoacetate, Serum or Plasma

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
**Acetylcholine Receptor (Muscle AChR) Binding Antibody, Serum**

**Clinical Information:** Myasthenia gravis (MG) is characterized by weakness and easy fatigability that are relieved by rest and anticholinesterase drugs. The weakness in most cases results from an autoantibody-mediated loss of functional acetylcholine receptors (AChR) in the postsynaptic membrane of skeletal muscle. Demonstration of muscle AChR autoantibodies in a patient’s serum supports the diagnosis of acquired (autoimmune) MG, and quantitation provides a baseline for future comparisons. Muscle AChR antibodies are not found in congenital forms of MG and are uncommon in neurologic conditions other than acquired MG, with the exception of patients with paraneoplastic autoimmunity neurological disorders, and Lambert-Eaton myasthenic syndrome (LES) with or without cancer (13% of LES patients have positive results for muscle AChR binding or striational antibodies). Patients with autoimmune liver disease are also frequently seropositive. The assay for muscle AChR binding antibodies is considered a first-order test for the laboratory diagnosis of MG, and for detecting "subclinical MG" in recipients of D-penicillamine, in patients with thymoma without clinical evidence of MG, and in patients with graft-versus-host disease.

**Useful For:** A first-order test for the laboratory diagnosis of myasthenia gravis (MG) Detecting "subclinical MG" in recipients of D-penicillamine, in patients with thymoma without clinical evidence of MG, and in patients with graft-versus-host disease Distinguishing acquired disease (90% positive) from congenital disease (negative) Monitoring disease progression in MG or response to immunotherapy An adjunct to the test for P/Q-type calcium channel binding antibodies as a diagnostic aid for Lambert-Eaton myasthenic syndrome (LES) or primary lung carcinoma

**Interpretation:** Values above 0.02 nmol/L are consistent with a diagnosis of acquired myasthenia gravis (MG), provided that clinical and electrophysiological criteria support that diagnosis. The assay for muscle acetylcholine receptor (AChR) binding antibodies is positive in approximately 90% of nonimmunosuppressed patients with generalized MG. The frequency of antibody detection is lower in MG patients with weakness clinically restricted to ocular muscles (71%), and antibody titers are generally low in ocular MG (eg, 0.03-1.0 nmol/L). Results may be negative in the first 12 months after symptoms of MG appear or during immunosuppressant therapy. Note: In follow up of seronegative patients with adult-acquired generalized MG, 17.4% seroconvert to positive at 12 months (ie, seronegativity rate at 12 months is 8.4%). Of persistently seronegative patients, 38% have muscle-specific kinase (MuSK) antibody. Sera of nonmyasthenic subjects bind 0.02 nmol/L or less of muscle AChR complexed with (125)I-labeled-alpha-bungarotoxin. In general, there is not a close correlation between antibody titer and severity of weakness, but in individual patients, clinical improvement is usually accompanied by a decrease in titer.

**Reference Values:**
< or =0.02 nmol/L

along the brain and spine. They develop in the early embryonic period when the neural tube fails to completely close. NTD can vary widely in severity. Anencephaly represents the most severe type of NTD. This occurs when the cranial end fails to develop properly, resulting in an absence of the forebrain, the area of the skull that covers the brain, and the skin. Most infants with anencephaly are stillborn or die shortly after birth. NTD along the spine are referred to as spina bifida. Individuals with spina bifida may experience hydrocephalus, urinary and bowel dysfunction, club foot, lower body weakness, and loss of feeling or paralysis. Severity varies depending upon whether the NTD is covered by skin, whether herniation of the meninges and spinal cord are present, and the location of the lesion. NTD not covered by skin are referred to as open NTD and are typically more severe than closed NTD. Likewise those presenting with herniation and higher on the spinal column are typically more severe. Most NTD occur as isolated birth defects with an incidence of approximately 1 to 2 in 1,000 live births in the United States. Rates vary by geographic region with lower rates being observed in the North and West than the South and East. A fetus is at higher risk when the pregnancy is complicated by maternal diabetes, exposed to certain anticonvulsants, or there is a family history of NTD. Studies have shown a dramatic decrease in risk as a result of maternal dietary supplementation with folic acid. The March of Dimes currently recommends that all women of childbearing age take 400 mcg of folic acid daily, increasing the amount to 600 mcg/day during pregnancy. For women who have had a prior pregnancy affected by an NTD, the recommended dose is at least 4,000 mcg/day starting at least 1 month preconception and continuing through the first trimester. When an NTD is suspected based upon maternal serum alpha-fetoprotein (AFP) screening results or diagnosed via ultrasound, analysis of alpha-fetoprotein (AFP) and acetylcholinesterase (AChE) in amniotic fluid are useful diagnostic tools. AChE is primarily active in the central nervous system with small amounts of enzyme found in erythrocytes, skeletal muscle, and fetal serum. Normal amniotic fluid does not contain AChE, unless contributed by the fetus as a result of an open NTD.

**Useful For:** Diagnosing open neural tube defects and, to a lesser degree, ventral wall defects

**Interpretation:** The presence of acetylcholinesterase in amniotic fluid is consistent with open neural tube defects and, to a lesser degree, ventral wall defects.

**Reference Values:**
Negative (reported as negative [normal] or positive [abnormal] for inhibitable acetylcholinesterase)

Reference values were established in conjunction with alpha-fetoprotein testing and include only amniotic fluids from pregnancies between 14 and 21 weeks gestation.


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**Acetylcholinesterase, Erythrocytes**

**Clinical Information:** Acetylcholinesterase (AChE) is anchored to the external surface of the RBC. Its appearance in a lysate of red cells is diminished in paroxysmal nocturnal hemoglobinuria (PNH). The use of red cell AChE for PNH has not gained widespread acceptance, and flow cytometry testing is most often used for PNH (see PANH/81156 PI-Linked Antigen, Blood). Red cell AChE is most often used to detect past exposure to organophosphate insecticides with resultant inhibition of the enzyme. Both the pseudocholinesterase activity in serum and red cell AChE are inhibited by these insecticides, but they are dramatically different vis-a-vis the temporal aspect of the exposure. The half-life of the pseudo-enzyme in serum is about 8 days, and the “true” cholinesterase (AChE) of red cells is over 3 months (determined by erythropoietic activity). Recent exposure up to several weeks is determined by assay of the pseudo-enzyme and months after exposure by measurement of the red cell enzyme. The effect of the specific insecticides may be important to know prior to testing.

**Useful For:** Detecting effects of remote (months) past exposure to cholinesterase inhibitors (organophosphate insecticide poisoning)

**Interpretation:** Activities less than normal are suspect for exposure to certain insecticides.

**Reference Values:**

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ACHS

8522

Achaete-Scute Homolog 1 (ACSL1) (hASH1) Immunostain, Technical Component Only

Clinical Information: Achaete-scute homolog 1 (ACSL1), alternatively titled hASH1 or MASH1, is a member of the basic helix-loop-helix family of transcription factors. ACSL1 may play a role at early stages of development of specific neural lineages in most regions of the central nervous system, and of several lineages in the peripheral nervous system. The protein has been shown to be highly expressed in medullary thyroid cancer and small cell lung cancer and may be a useful marker for these cancers.

Useful For: Identification of the presence of Achaete-scute homolog 1 (ACSL1)

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Acid Alpha-Glucosidase, Blood Spot

Clinical Information: Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme alpha-glucosidase (GAA). This leads to an accumulation of glycogen in the lysosome causing swelling, cell damage, and progressive organ dysfunction. Pompe disease is caused by mutations in the GAA gene, and it is characterized by muscle hypotonia, weakness, cardiomegaly, hypertrophic cardiomyopathy, and eventual death due to either cardiorespiratory or respiratory failure. The clinical phenotype, in general, appears to be dependent on residual enzyme activity, with complete loss of activity causing onset in infancy. Untreated, this leads to death, typically within the first year of life. Juvenile and adult-onset forms are characterized by later onset and longer survival. Primary symptoms of later-onset Pompe disease include muscle weakness and respiratory insufficiency. Rarely, clinically significant cardiomyopathy can be seen. The estimated incidence is 1 in 40,000 live births. Enzyme replacement therapy (ERT) improves outcome in many patients with either classic infantile onset or later onset forms of Pompe disease. Early initiation of treatment improves the prognosis and makes early diagnosis of
Pompe disease desirable. Because of this, newborn screening for Pompe disease has recently been implemented in some states. The early identification and treatment of infants with Pompe disease has been shown to be helpful in reducing the morbidity and mortality associated with this disease. Since Pompe disease is considered a rare condition that progresses rapidly in infancy, the disease, in particular the juvenile and adult-onset forms, is often considered late if at all, during the evaluation of patients presenting with proximal muscle weakness and respiratory insufficiency. Testing traditionally required a skin or muscle biopsy to establish cultures for enzyme testing. More recently, molecular genetic testing of the GAA gene (GAAZ / Pompe Disease, Full Gene Analysis) became clinically available. Determination of the enzyme activity in dried blood spot specimens can be performed in a timely fashion and provide better guidance in the decision to submit samples for further confirmatory testing by molecular genetic analysis (GAAZ / Pompe Disease, Full Gene Analysis).

**Useful For:** Evaluation of patients of any age with a clinical presentation suggestive of Pompe disease (muscle hypotonia, weakness, or cardiomyopathy)

**Interpretation:** Normal results (>0.5 nmol/hour/mL) in properly submitted specimens are not consistent with classic Pompe disease. Affected individuals typically have levels of 0.5 nmol/hour/mL or less; however, some later onset cases may show higher enzyme activity. Results of 0.5 nmol/hour/mL or less can be followed up by molecular genetic analysis of the GAA gene (GAAZ / Pompe Disease, Full Gene Analysis) to determine carrier, pseudodeficiency, or disease status.

**Reference Values:**
Normal >0.5 nmol/mL/hour

**Clinical References:**

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**Acid-Fast Smear for Mycobacterium**

**Clinical Information:** Mycobacterium tuberculosis is a leading infectious disease cause of death worldwide. The Centers for Disease Control and Prevention has reported a rise in the incidence of tuberculosis associated with AIDS, foreign-born cases, and increased transmission in high-risk populations. There has also been a rise in the number of M tuberculosis strains that exhibit resistance to one or more antituberculosis drugs. The public health implications of these facts are considerable. Because M tuberculosis is readily spread by airborne particles, rapid diagnosis and isolation of infected persons is important. Nontuberculous mycobacteria infections also cause significant morbidity and mortality in humans, particularly in immunocompromised persons. Detection of acid-fast bacilli in sputum specimens allows rapid identification of individuals who are likely to be infected with mycobacteria while definitive diagnosis and treatment are pursued.

**Useful For:** Detection of acid-fast bacilli in clinical specimens

**Interpretation:** Patients whose sputum specimens are identified as acid-fast positive should be considered potentially infected with Mycobacterium tuberculosis, pending definitive diagnosis by molecular methods or mycobacterial culture.

**Reference Values:**
Negative (reported as positive or negative)

**Clinical References:**
Actin, Smooth Muscle (SMActin) Immunostain, Technical Component Only

**Clinical Information:** Smooth muscle actin reacts with the alpha-smooth muscle isoform of actin, and labels the smooth muscle cells of vessels, myoepithelial cells, pericytes, some stromal cells in the intestine, testis, and ovary, and tumors derived from smooth muscle cells. The antibody does not react with actin from fibroblasts, striated muscle, and myocardium. This immunostain is a useful tool in the identification of leiomyomas, leiomyosarcomas, and pleomorphic adenomas.

**Useful For:** Identification of cells expressing the alpha-smooth muscle isoform of actin

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

Actinomyces Culture

**Clinical Information:** Anaerobic Actinomyces are nonsporeforming, thin branching, gram-positive bacilli that are part of the normal flora of the human oral cavity and may also colonize the gastrointestinal and female genital tracts. Their presence is important in preserving the usual bacterial populations of the mouth and in preventing infection with pathogenic bacteria. Actinomyces are generally of low pathogenicity but may be an important factor in the development of periodontal disease and may cause soft tissue infections in colonized areas of the body following trauma (surgical or otherwise). The typical lesion consists of an outer zone of granulation around central purulent loculations containing masses of tangled organisms ("sulfur granule"). Chronic burrowing sinus tracts develop. Typical actinomycotic infections occur around the head and neck, in the lung and chest wall, and in the peritoneal cavity and abdominal wall. Actinomycosis of the female genital tract occurs in association with use of intrauterine contraceptive devices. Purulent collections containing "sulfur granules" may drain from some sinus tracts opening to the skin.

**Useful For:** Diagnosing anaerobic Actinomyces involved in infections

**Interpretation:** Isolation of anaerobic Actinomyces in significant numbers from well collected specimens including blood, other normally sterile body fluids, or closed collections of purulent fluid indicates infection with the identified organism.
Reference Values:
No growth
Identification of probable pathogens

Clinical References:

**Activated Partial Thromboplastin Time (APTT), Plasma**

**Clinical Information:** The activated partial thromboplastin time (APTT) assay is used as a screening test to evaluate the overall integrity of the intrinsic/common coagulation pathway and to monitor patients on heparin therapy. This test reflects the activities of most of the coagulation factors in the intrinsic and common procoagulant pathway, but not the extrinsic procoagulant pathway, which includes factor VII and tissue factor, nor the activity of factor XIII (fibrin stabilizing factor). Effective November 2016, APTT will no longer be used as the primary method for therapeutic heparin monitoring, for that purpose, order the heparin anti-Xa assay HEPPT / Heparin Anti-Xa Assay, Plasma.

**Useful For:** Monitoring heparin therapy (unfractionated heparin) Screening for certain coagulation factor deficiencies Detection of coagulation inhibitors such as lupus anticoagulant, specific factor inhibitors, and nonspecific inhibitors

**Interpretation:** Prolongation of the activated partial thromboplastin time (APTT) can occur as a result of deficiency of one or more coagulation factors (acquired or congenital in origin), or the presence of an inhibitor of coagulation such as heparin, a lupus anticoagulant, a nonspecific inhibitor such as a monoclonal immunoglobulin, or a specific coagulation factor inhibitor. Prolonged clotting times may also be observed in cases of fibrinogen deficiency, liver disease, and vitamin K deficiency. Shortening of the APTT usually reflects either elevation of factor VIII activity in vivo that most often occurs in association with acute or chronic illness or inflammation, or spurious results associated with either difficult venipuncture and specimen collection or suboptimal specimen processing.

**Reference Values:**
25-37 seconds

**Clinical References:**

**Activated Protein C Resistance V (APCRV), Plasma**

**Clinical Information:** Protein C, a part of the natural anticoagulant system, is a vitamin K-dependent protein zymogen (molecular weight=62,000 da) that is synthesized in the liver and circulates at a plasma concentration of approximately 5 mcg/mL. Protein C is activated to activated protein C (APC) via proteolytic cleavage by thrombin bound to thrombomodulin, an endothelial cell surface membrane protein. APC downregulates the procoagulant system by proteolytically inactivating procoagulant factors Va and VIIIa. Protein S, another vitamin K-dependent coagulation protein, catalyzes APC inactivation of factors Va and VIIIa. APC interacts with and proteolyses factors V/Va and VIII/VIIIa at specific APC binding and cleavage sites, respectively. Resistance to activated protein C (APC resistance) is a term used to describe abnormal resistance of human plasma to the anticoagulant effects of human APC. APC resistance is characterized by a reduced anticoagulant response of patient plasma after adding a standard amount of APC. For this assay, the activated partial thromboplastin time clotting test fails to prolong significantly after the addition of APC. The vast majority of individuals with familial APC resistance have...
a specific point mutation in the procoagulant factor V gene (1691G-A, factor V Leiden) encoding for a glutamine (Q) substitution for arginine (R)-506 in the heavy chain of factor V (factor V R506Q). This amino acid change alters an APC cleavage site on factor V such that factor V/Va is partially resistant to inactivation by APC. The carrier frequency for the factor V Leiden mutation varies depending on the population. Approximately 5% of asymptomatic white Americans of non-Hispanic ancestry are heterozygous carriers, while the carrier frequency among African Americans, Asian Americans, and Native Americans is less than 1%, and the carrier frequency for Hispanics is intermediate (2.5%). The carrier frequency can be especially high (up to 14%) among whites of Northern European or Scandinavian ancestry. Homozygosity for factor V Leiden is much less common, but may confer a substantially increased risk for thrombosis. The degree of abnormality of the APC-resistance assay correlates with heterozygosity or homozygosity for the factor V Leiden mutation; homozygous carriers have a very low APC-resistance ratio (eg, 1.1-1.4), while the ratio for heterozygous carriers is usually 1.5 to 1.8.

**Useful For:** Evaluation of patients with incident or recurrent venous thromboembolism (VTE)
Evaluation of individuals with a family history of VTE

**Interpretation:** An activated protein C (APC) resistance ratio of less than 2.3 suggests abnormal resistance to APC of hereditary origin. If the APC resistance test is abnormal, DNA-based testing for the factor V Leiden mutation (F5DNA / Factor V Leiden [R506Q] Mutation, Blood) may be helpful in confirming or excluding hereditary APC-resistance.

**Reference Values:**
APCRV RATIO
> or =2.3
Pediatric reference range has neither been established nor is available in scientific literature. The adult reference range likely would be applicable to children older than 6 months.

**Clinical References:**

---

**Activated Protein C Resistance V (APCRV), with Reflex to Factor V Leiden, Plasma**

**Clinical Information:** Protein C, a part of the natural anticoagulant system, is a vitamin K-dependent protein zymogen (molecular weight=62,000 da) that is synthesized in the liver and circulates at a plasma concentration of approximately 5 mcg/mL. Protein C is activated to activated protein C (APC) via proteolytic cleavage by thrombin bound to thrombomodulin, an endothelial cell surface membrane protein. APC downregulates the procoagulant system by proteolytically inactivating procoagulant factors Va and VIIIa. Protein S, another vitamin K-dependent coagulation protein, catalyzes APC inactivation of factors Va and VIIIa. APC interacts with and proteolyses factors V/Va and VIII/VIIIa at specific APC binding and cleavage sites, respectively. Resistance to activated protein C (APC resistance) is a term used to describe abnormal resistance of human plasma to the anticoagulant effects of human APC. APC resistance is characterized by a reduced anticoagulant response of patient plasma after adding a standard amount of APC. For this assay, the activated partial thromboplastin time clotting test fails to prolong significantly after the addition of APC. The vast majority of individuals with familial APC resistance have a specific point mutation in the procoagulant factor V gene (1691G-A, factor V Leiden) encoding for a glutamine (Q) substitution for arginine (R)-506 in the heavy chain of factor V (factor V R506Q). This amino acid change alters an APC cleavage site on factor V such that factor V/Va is partially resistant to inactivation by APC. The carrier frequency for the factor V Leiden mutation varies depending on the population. Approximately 5% of asymptomatic
white Americans of non-Hispanic ancestry are heterozygous carriers, while the carrier frequency among African Americans, Asian Americans, and Native Americans is <1%, and the carrier frequency for Hispanics is intermediate (2.5%). The carrier frequency can be especially high (up to 14%) among whites of Northern European or Scandinavian ancestry. Homozygosity for factor V Leiden is much less common, but may confer a substantially increased risk for thrombosis. The degree of abnormality of the APC-resistance assay correlates with heterozygosity or homozygosity for the factor V Leiden mutation; homozygous carriers have a very low APC-resistance ratio (eg, 1.1-1.4), while the ratio for heterozygous carriers is usually 1.5 to 1.8.

**Useful For:** Evaluation of patients with incident or recurrent venous thromboembolism (VTE)
Evaluation of individuals with a family history of VTE

**Interpretation:** An activated protein C (APC) resistance ratio of below 2.3 suggests abnormal resistance to APC of hereditary origin. If the screening APC resistance test is abnormal, DNA-based testing for the factor V Leiden mutation F5DNA / Factor V Leiden (R506Q) Mutation, Blood is performed to confirm or exclude hereditary APC-resistance.

**Reference Values:**
APCRV RATIO

> or =2.3

Pediatric reference range has neither been established nor is available in scientific literature. The adult reference range likely would be applicable to children older than 6 months.

**Clinical References:**

**Acute Hepatitis Profile**

**Clinical Information:** Hepatitis A: Hepatitis A virus (HAV) is an RNA virus that accounts for 20% to 25% of the viral hepatitis in United States adults. HAV infection is spread by the oral/fecal route and produces acute hepatitis that follows a benign, self-limited course. Spread of the disease is usually associated with contaminated food or water caused by poor sanitary conditions. Outbreaks frequently occur in overcrowded situations and in institutions or high-density centers such as prisons and health care centers. Epidemics may occur following floods or other disaster situations. Chronic carriers of HAV have never been observed. Hepatitis B: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (eg, blood transfusion, sharing of needles by drug addicts). The virus is also found in virtually every type of human body fluid and is known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions; it is not commonly transmitted transplacentally. After a course of acute illness, HBV persists in approximately 10% of patients. Some of these chronic carriers are asymptomatic others develop chronic liver disease, including cirrhosis and hepatocellular carcinoma. Hepatitis C: Hepatitis C virus (HCV) is an RNA virus that is a significant cause of morbidity and mortality worldwide. HCV is transmitted through contaminated blood or blood products or through other close, personal contacts. It is recognized as the cause of most cases of posttransfusion hepatitis. HCV shows a high rate of progression (>50%) to chronic disease. In the United States, HCV infection is quite common, with an estimated 3.5 to 4 million chronic HCV carriers. Cirrhosis and hepatocellular carcinoma are sequelae of chronic HCV. The following algorithms are available in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -Hepatitis C: Testing Algorithm for Screening and Diagnosis -Viral Hepatitis Serologic Profiles
Useful For: Differential diagnosis of recent acute viral hepatitis

Interpretation: Hepatitis A: Antibody against hepatitis A antigen is usually detectable by the onset of symptoms (usually 15-45 days after exposure). The initial antibody consists almost entirely of IgM subclass antibody. Antibody to hepatitis A virus (anti-HAV) IgM usually falls to undetectable levels 3 to 6 months after infection. Hepatitis B: Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum 6 to 16 weeks following hepatitis B virus (HBV) infection. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Hepatitis B surface antibody (anti-HBs) appears with the resolution of HBV infection after the disappearance of HBsAg. Anti-HBs also appears as the immune response following a course of inoculation with the hepatitis B vaccine. Initially, hepatitis B core antibody (anti-HBc) consists almost entirely of the IgM subclass. Anti-HBc, IgM can be detected shortly after the onset of symptoms and is usually present for 6 months. Anti-HBc may be the only marker of a recent HBV infection detectable following the disappearance of HBsAg, and prior to the appearance of anti-HBs, ie, window period. Hepatitis C: Hepatitis C antibody is usually not detectable during the early months following infection and is almost always detectable by the late convalescent stage of infection. Hepatitis C antibody is not neutralizing and does not provide immunity. If HBsAg, anti-HAV (IgM), and anti-HCV are negative and patient's condition warrants, consider testing for Epstein-Barr virus or cytomegalovirus. The following algorithms are available in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -Hepatitis C: Testing Algorithm for Screening and Diagnosis

Reference Values:
HEPATITIS B SURFACE ANTIGEN
Negative

HEPATITIS B SURFACE ANTIGEN CONFIRMATION
Negative

HEPATITIS B CORE IgM ANTIBODY
Negative

HEPATITIS A IgM ANTIBODY
Negative

HEPATITIS C ANTIBODY
Negative

HEPATITIS C VIRUS RNA DETECTION and QUANTIFICATION by REAL-TIME RT-PCR
Undetected

Interpretation depends on clinical setting. See Viral Hepatitis Serologic Profiles in Special Instructions.


AMLF 35255

Acute Myeloid Leukemia (AML), FISH

Clinical Information: Acute myeloid leukemia (AML) is one of the most common adult leukemias, with almost 10,000 new cases diagnosed per year. AML also comprises 15% of pediatric acute leukemia and accounts for the majority of infant (<1 year old) leukemia. Several subtypes of AML have been recognized (termed AML-M0, M1, M2, M3, M4, M5, M6, and M7) based on the cell morphology...
and myeloid lineage involved. In addition to morphology, several recurrent chromosomal abnormalities have been linked to specific subtypes of AML. The most common chromosome abnormalities associated with AML include t(8;21), t(15;17), inv(16), +8, t(6;9), t(8;16), t(1;22), t(9;22), t(3;5), and abnormalities of the MLL (KMT2A) gene at 11q23. The most common genes juxtaposed with MLL through translocation events in AML include AFF1-t(4;11), MLLT4-t(6;11), MLLT3-t(9;11), MLLT10-t(10;11), CREBBP-t(11;16), ELL-t(11;19p13.1), and MLLT1-t(11;19p13.3). AML can also evolve from myelodysplasia (MDS). Thus, the common chromosome abnormalities associated with MDS can also be identified in AML, which include: inv(3), -5/5q-, -7/7q-, +8, 13q-, 17p-, 20q-, t(1;3), and t(3;21). In combination, the multiple recurrent chromosome abnormalities identified in patients with AML are observed in approximately 60% of diagnostic AML cases. Conventional chromosome analysis is the gold standard for identification of the common, recurrent chromosome abnormalities in AML, however, some of the subtle rearrangements can be missed: eg, inv(16), MLL and NUP98 abnormalities. FISH analysis of nonproliferating (interphase) cells can be used to detect the common chromosome abnormalities observed in patients with AML. The abnormalities have diagnostic and prognostic relevance and this testing can also be used to track response to therapy.

**Useful For:** Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with acute myeloid leukemia or other myeloid malignancies Evaluating specimens in which standard cytogenetic analysis is unsuccessful Identifying and tracking known chromosome abnormalities in patients with myeloid malignancies and tracking response to therapy

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. Detection of an abnormal clone likely indicates a diagnosis of an acute myeloid leukemia of various subtypes. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Acute Porphyria, Multi-Gene Panel**

**Clinical Information:** Acute porphyria is caused by autosomal dominant mutations in 1 of 3 genes: HMBS, associated with acute intermittent porphyria (AIP); CPOX, associated with hereditary coproporphyria (HCP); and PPOX, associated with variegate porphyria (VP). Mutations in these genes show incomplete penetrance, and patients with a confirmed deleterious mutation may be asymptomatic. Clinical manifestations of acute porphyria include attacks of neurologic dysfunction, commonly characterized as abdominal pain. However, these acute attacks are variable and can include vomiting, diarrhea, constipation, urinary retention, acute episodes of neuropathic symptoms, psychiatric symptoms, seizures, respiratory paralysis, tachycardia, and hypertension. Respiratory paralysis can progress to coma and death. HCP and VP are also associated with cutaneous manifestations, including edema, sun-induced erythema, acute painful photodermatitis, and urticaria. In some cases, patients present with isolated photosensitivity. Acute attacks may be prevented by avoiding both endogenous and exogenous triggers. These triggers include porphyrigenic drugs, hormonal contraceptives, fasting, alcohol, tobacco, and cannabis. Fecal porphyrins analysis and quantitative urinary porphyrins analysis are helpful in establishing a diagnosis of acute porphyria.

**Useful For:** Confirmation of acute porphyria for patients with clinical features of the disease

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible
pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FACY**

90308

**Acyclovir, Serum/Plasma**

**Reference Values:**
Reporting limit determined each analysis

**Synonym(s):** Zovirax

Usual therapeutic range (vs. Genital Herpes) during chronic oral daily divided dosages of 1200 â€“ 2400 mg:

- Peak: 0.40 â€“ 2.0 mcg/mL plasma
- Trough: 0.14 â€“ 1.2 mcg/mL plasma

**ACRN**

82413

**Acylcarnitines, Quantitative, Plasma**

**Clinical Information:** Acylcarnitine analysis enables the diagnosis of many disorders of fatty acid oxidation and several organic acidurias, as relevant enzyme deficiencies cause the accumulation of specific acyl-CoAs. Fatty acid oxidation (FAO) plays a major role in energy production during periods of fasting. When the body's supply of glucose is depleted, fatty acids are mobilized from adipose tissue, taken up by the liver and muscles, and oxidized to acetyl-CoA. In the liver, acetyl-CoA is the building block for the synthesis of ketone bodies, which enter the blood stream and provide an alternative substrate for production of energy in other tissues when the supply of glucose is insufficient to maintain a normal level of energy. The acyl groups are conjugated with carnitine to form acylcarnitines, which are measured by tandem mass spectrometry (MS/MS). Diagnostic results are usually characterized by a pattern of significantly elevated acylcarnitine species compared to normal and disease controls. In general, more than 20 inborn errors of metabolism can be identified using this method including FAO disorders and organic acidurias. The major clinical manifestations associated with individual FAO disorders include hypoketotic hypoglycemia, variable degrees of liver disease and failure, skeletal myopathy, dilated/hypertrophic cardiomyopathy, and sudden or unexpected death. Organic acidurias also present as acute life-threatening events early in life with metabolic acidosis, increased anion gap, and neurologic distress. Patients with any of these disorders are at risk of developing fatal metabolic decompensations following the acquisition of even common infections. Once diagnosed, these disorders can be treated by avoidance of fasting, special diets, and cofactor and vitamin supplementation. Analysis of acylcarnitines in blood and bile spots represents the first level of evaluation of a complete postmortem investigation of a sudden or unexpected death of an individual. Additional confirmatory testing is recommended. The diagnosis of an underlying FAO disorder or organic aciduria allows genetic counseling of the family, including the possible option of future prenatal diagnosis, and testing of at-risk family members of any age. Disorders Detectable by Acylcarnitine Analysis* Fatty Acid Oxidation Disorders: -Carnitine palmitoyltransferase I (CPTI) deficiency  -Medium-chain 3-ketoacyl-CoA thiolase (MCKAT) deficiency  -Diensoyl-CoA reductase deficiency  -Short-chain acyl-CoA dehydrogenase (SCAD) deficiency  -Medium/Short-chain 3-hydroxyacyl-CoA dehydrogenase (M/SCHAD) deficiency  -Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency  -Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency & trifunctional protein deficiency  -Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency  -Carnitine palmitoyl transferase type II (CPT-II) deficiency  -Carnitine-acylcarnitine translocase (CACT) deficiency  -Electron transfer...
flavoprotein (ETF) deficiency, ETF-dehydrogenase deficiency (multiple acyl-CoA dehydrogenase deficiency [MADD]; glutaric acidemia type II) Organic Acid Disorders: -Glutaryl-CoA dehydrogenase deficiency (glutaric acidemia type I) -Propionic Acidemia -Methylmalonic Acidemia -Isovaleric Acidemia -3-hydroxy-3-methylglutaryl-CoA carboxylase deficiency -3-Methylcrotonyl carboxylase deficiency -Biotinidase deficiency -Multiple carboxylase deficiency -Isobutyryl-CoA dehydrogenase deficiency -2-Methylbutyryl-CoA dehydrogenase deficiency -Beta-ketothiolase deficiency -Malonic aciduria -Ethylmalonic encephalopathy -Glutamate formiminotransferase deficiency (Formiminoglutaric aciduria) *Further confirmatory testing is required for most of these conditions because an acylcarnitine profile can be suggestive of more than 1 condition.

Useful For: Diagnosis of fatty acid oxidation disorders and several organic acidurias in plasma specimens Evaluating treatment during follow-up of patients with fatty acid beta-oxidation disorders and several organic acidurias

Interpretation: An interpretive report is provided. The individual quantitative results support the interpretation of the acylcarnitine profile but are not diagnostic by themselves. The interpretation is based on pattern recognition. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on an acylcarnitine analysis, independent biochemical (eg, in vitro enzyme assay) or molecular genetic analyses are required. For information on the follow-up of specific acylcarnitine elevations, see Special Instructions for the following algorithms: -Newborn Screening Follow-up for Elevations of C8, C6, and C10 Acylcarnitines (also applies to any plasma or serum C8, C6, and C10 acylcarnitine elevations) -Newborn Screening Follow-up for Isolated C4 Acylcarnitine Elevations (also applies to any plasma or serum C4 acylcarnitine elevation) -Newborn Screening Follow-up for Isolated C5 Acylcarnitine Elevations (also applies to any plasma or serum C5 acylcarnitine elevation)

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<th>&gt; or =8 years (nmol/mL)</th>
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Dodecanoylcarnitine, C12
3-Methylglutaryl carnitine, C6-DC
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3-OH-dodecanoylcarnitine, C12-OH
Tetradecadienoylcarnitine, C14:2
Tetradecenoylcarnitine, C14:1
Tetradecanoylcarnitine, C14
Octanediolcarnitine, C8-DC
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Hexadecenoylcarnitine, C16:1
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Octadecenoylcarnitine, C18:1
Octadecanoylcarnitine, C18
Dodecanedioylcarnitine, C12-DC
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3-OH-octadecenoylcarnitine C18:1-OH
3-OH-octadecanoylcarnitine, C18-OH


ACRNS 60644

Acylcarnitines, Quantitative, Serum

Clinical Information: Acylcarnitine analysis enables the diagnosis of many disorders of fatty acid oxidation and several organic acidurias, as relevant enzyme deficiencies cause the accumulation of specific acyl-CoAs. Fatty acid oxidation (FAO) plays a major role in energy production during periods of fasting. When the body's supply of glucose is depleted, fatty acids are mobilized from adipose tissue, taken up by the liver and muscles, and oxidized to acetyl-CoA. In the liver, acetyl-CoA is the building block for the synthesis of ketone bodies, which enter the blood stream and provide an alternative energy source.
substrate for production of energy in other tissues when the supply of glucose is insufficient to maintain a normal level of energy. The acyl groups are conjugated with carnitine to form acylcarnitines, which are measured by tandem mass spectrometry (MS/MS). Diagnostic results are usually characterized by a pattern of significantly elevated acylcarnitine species compared to normal and disease controls. In general, more than 20 inborn errors of metabolism can be identified using this method including FAO disorders and organic acidurias. The major clinical manifestations associated with individual FAO disorders include hypoketotic hypoglycemia, variable degrees of liver disease and/or failure, skeletal myopathy, dilated/hypertrophic cardiomyopathy, and sudden or unexpected death. Organic acidurias also present as acute life-threatening events early in life with metabolic acidosis, increased anion gap, and neurologic distress. Patients with any of these disorders are at risk of developing fatal metabolic decompensations following the acquisition of even common infections. Once diagnosed, these disorders can be treated by avoidance of fasting, special diets, and cofactor/vitamin supplementation. Analysis of acylcarnitines in blood and bile spots represents the first level of evaluation of a complete postmortem investigation of a sudden or unexpected death of an individual. Additional confirmatory testing is recommended. The diagnosis of an underlying FAO disorder or organic aciduria allows genetic counseling of the family, including the possible option of future prenatal diagnosis, and testing of at-risk family members of any age. Disorders Detectable by Acylcarnitine Analysis* Fatty Acid Oxidation Disorders: Carnitine palmitoyltransferase I (CPTI) deficiency Medium-chain 3-ketoacyl-CoA thiolase (MCKAT) deficiency Dienoyl-CoA reductase deficiency Short-chain acyl-CoA dehydrogenase (SCAD) deficiency -Medium/Short-chain 3-hydroxyacyl-CoA dehydrogenase (M/SCHAD) deficiency -Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency -Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency & trifunctional protein deficiency -Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency -Carnitine palmitoyl transferase type II (CPT-II) deficiency -Car

Acetylcarnitine, C2 2.14-15.89 2.00-27.57 2.00-17.83
Acrylylcarnitine, C3:1
Propionylcarnitine, C3
Formiminoglutamate, FIGLU

Useful For: Diagnosis of fatty acid oxidation disorders and several organic acidurias in serum specimens Evaluating treatment during follow-up of patients with fatty acid beta-oxidation disorders and several organic acidurias

Interpretation: An interpretive report is provided. The individual quantitative results support the interpretation of the acylcarnitine profile but are not diagnostic by themselves. The interpretation is based on pattern recognition. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on an acylcarnitine analysis, independent biochemical (eg, in vitro enzyme assay) or molecular genetic analyses are required. For information on the follow-up of specific acylcarnitine elevations, see Special Instructions for the following algorithms: -Newborn Screening Follow-up for Elevations of C8, C6, and C10 Acylcarnitines (also applies to any plasma or serum C8, C6, and C10 acylcarnitine elevations) -Newborn Screening Follow-up for Isolated C4 Acylcarnitine Elevations (also applies to any plasma or serum C4 acylcarnitine elevation) -Newborn Screening Follow-up for Isolated C5 Acylcarnitine Elevations (also applies to any plasma or serum C5 acylcarnitine elevation)

Reference Values:
Iso-/Butyrylcarnitine, C4
Tiglylcarnitine, C5:1
Isovaleryl/-2-Methylbutyrylcarn C5
3-OH-is-/butyrylcarnitine, C4-OH
Hexenoylcarnitine, C6:1
Hexanoylcarnitine, C6
3-OH-isovalerylcarnitine, C5-OH
Benzoylcarnitine
Heptanoylcarnitine, C7
3-OH-hexanoylcarnitine, C6-OH
Phenylacetylcarnitine
Salicylcarnitine
Octenoylcarnitine, C8:1
Octanoylcarnitine, C8
Malonylcarnitine, C3-DC
Decadienoylcarnitine, C10:2
Decenoylcarnitine, C10:1
Decanoylcarnitine, C10
Methylmalonyl/-succinylcarn, C4-DC
3-OH-decenoylcarnitine, C10:1-OH
Glutarylcarntine, C5-DC
Dodecenoylcarnitine, C12:1
Dodecanoylcarnitine, C12
3-Methylglutarylcarntine, C6-DC
3-OH-dodecenoylcarnitine, C12:1-OH
3-OH-dodecanoylcarnitine, C12-OH
Tetradecadienoylcarnitine, C14:2
Tetradecenoylcarnitine, C14:1
Tetradecanoylcarnitine, C14
Octanediylcarnitine, C8-DC
3-OH-tetradecenoylcarnitine C14:1OH
3-OH-tetradecanoylcarnitine, C14-OH
Hexadecenoylcarnitine, C16:1
Hexadecanoylcarnitine, C16
3-OH-hexadecenoylcarnitine, C16:1-OH
3-OH-hexadecanoylcarnitine, C16-OH
Octadecadienoylcarnitine, C18:2
Octadecenoylcarnitine, C18:1
Octadecanoylcarnitine, C18
Dodecanedioylcarnitine, C12-DC
3-OH-octadecadienoylcarn, C18:2-OH
3-OH-octadecenoylcarnitine C18:1-OH
3-OH-octadecanoylcarnitine, C18-OH


Acylglycines, Quantitative, Urine

Clinical Information: Acylglycines are glycine conjugates of acyl-CoA species. Acylglycines are normal intermediates of amino acid and fatty acid metabolism; however, in abnormal concentrations acylglycines are biochemical markers of selected inborn errors of metabolism (IEM). Analysis of acylglycines is a useful screening test in the evaluation of patients with a suspected IEM, though additional studies are necessary to establish a diagnosis. The biochemical diagnosis of these disorders is a complex process achieved by multiple tests and their integrated interpretation. Although acylglycines are often ordered in conjunction with organic acids, acylglycine analysis is more sensitive and specific for the identification of asymptomatic patients and those with mild or intermittent biochemical phenotypes that could be missed by organic acid analysis alone. The quantitative analysis of urinary acylglycines is particularly effective for identifying asymptomatic patients affected with disorders including: -Short chain acyl-CoA dehydrogenase (SCAD) deficiency -Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency -Medium-chain 3-ketoacyl-CoA thiolase (MCKAT) deficiency -Glutaric acidemia type II -Ethylmalonic encephalopathy -2-Methylbutyryl-CoA dehydrogenase deficiency -Isovaleryl-CoA dehydrogenase deficiency -Glutaryl-CoA dehydrogenase deficiency

Useful For: Biochemical screening of asymptomatic patients affected with 1 of the following inborn errors of metabolism: -Short chain acyl-CoA dehydrogenase (SCAD) deficiency -Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency -Medium-chain 3-ketoacyl-CoA thiolase (MCKAT) deficiency -Glutaric acidemia type II -Ethylmalonic encephalopathy -2-Methylbutyryl-CoA dehydrogenase deficiency -Isovaleryl-CoA dehydrogenase deficiency -Glutaryl-CoA dehydrogenase deficiency

Interpretation: When abnormal results are detected, a detailed interpretation is given including an overview of the results and of their significance; a correlation to available clinical information; elements of differential diagnosis; recommendations for additional biochemical testing and in vitro confirmatory studies (enzyme assay, molecular analysis); name and phone number of key contacts who may provide these studies at Mayo Clinic or elsewhere; and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
Control Values Results Expressed as mg/g Creatinine

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Ethylmalonic Acid</td>
<td>0.5-20.2</td>
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<tr>
<td>2-Methylsuccinic Acid</td>
<td>0.4-13.8</td>
</tr>
<tr>
<td>Glutaric Acid</td>
<td>0.6-15.2</td>
</tr>
<tr>
<td>Isobutyrylglycine</td>
<td>0.00-11.0</td>
</tr>
<tr>
<td>n-Butyrylglycine</td>
<td>0.1-2.1</td>
</tr>
<tr>
<td>Chemical Name</td>
<td>Concentration Range</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>2-Methylbutyrylglycine</td>
<td>0.3-7.5</td>
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<tr>
<td>Isovalerylglycine</td>
<td>0.3-14.3</td>
</tr>
<tr>
<td>n-Hexanoylglycine</td>
<td>0.2-1.9</td>
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<tr>
<td>n-Octanoylglycine</td>
<td>0.1-2.1</td>
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<tr>
<td>3-Phenylpropionylglycine</td>
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<tr>
<td>Suberylglycine</td>
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<tr>
<td>trans-Cinnamoylglycine</td>
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<td>Dodecanedioic Acid (12 DCA)</td>
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</tr>
<tr>
<td>Tetradecanedioic Acid (14 DCA)</td>
<td>0.00-1.0</td>
</tr>
<tr>
<td>Hexadecanedioic Acid (16 DCA)</td>
<td>0.00-1.0</td>
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</tbody>
</table>

**Clinical References:**

**Adalimumab Quantitative with Reflex to Antibody, Serum**

**Clinical Information:** Adalimumab, sold under the trade name Humira, is a medication used to treat rheumatoid arthritis, psoriatic arthritis, Crohn disease, ulcerative colitis, chronic psoriasis, and others. Adalimumab is a tumor necrosis factor (TNF)-inhibiting, anti-inflammatory, biologic medication. It binds to tumor necrosis factor-alpha (TNF-alpha), which normally binds to TNF-alpha receptors, leading to the inflammatory response of autoimmune diseases. By binding to TNF-alpha, adalimumab reduces the inflammatory response. Because TNF-alpha is also part of the immune system, which protects the body from infection, treatment with adalimumab may increase the risk of infections. Treatment with adalimumab is effective in reducing disease activity, and offers significant benefits in quality of life and may have the potential to change the progression of the disease when given early. However, over 30% of patients fail to respond to anti-TNF-alpha therapy, and approximately 60% of patients who respond initially lose the response over time and require either drug dose-escalation or switch to an alternative agent in order to maintain response. Antidrug antibody formation may increase drug clearance in treated patients and/or neutralize the drug effect, thereby potentially contributing to the loss of response. Antidrug antibodies could also cause adverse events such as serum sickness and hypersensitivity reactions. Currently, adalimumab quantitation is commonly performed in conjunction with immunogenicity assessment for antibodies to adalimumab (ATA). Most often, this testing is ordered in patients on therapy who are experiencing loss of response. Results from drug concentration measurement combined with ATA testing play an important role in patient management. When measured at trough, for patients who have undetectable or low concentrations of drug but no detectable ATA, the physician may choose to increase the dose of adalimumab in an attempt to increase the amount of the drug in circulation. If the patient has low adalimumab in the presence of an ATA, in many cases the physician may switch the patient to another TNF inhibitor. In contrast, for patients with increased trough concentrations of adalimumab, whether or not an ATA is present, it may be necessary to switch the patient to a therapy with a different mechanism of action. For patients on biologics, assessing response to therapy is critical, since therapies are expensive and adverse events include greater risk for infections such as reactivation of latent tuberculosis or hepatitis B, infusion or injection site reactions, cutaneous reactions, and reports of hepatotoxicity, demyelinating disease, and higher incidence of mortality and hospitalization in patients with heart failure. Despite their therapeutic efficacy, more than one-third of patients on TNF inhibitors show no response to induction therapy (primary nonresponders) and, in up to 50% of the responders, therapy becomes ineffective over time.
(secondary nonresponders). Reasons for primary loss of response are not well understood, but may include disease processes mediated by proinflammatory molecules other than TNF. Secondary loss of response, on the other hand, is associated with low albumin, high body-mass index, the degree of systemic inflammation and immune response to therapy, or immunogenicity (development of autoantibodies against adalimumab). Laboratory testing of patients for quantitation of adalimumab and assessment of immunogenicity can help optimize therapy when partial response or loss of response to therapy is observed.

**Useful For:** Detection and quantification of antibodies directed against adalimumab in serum Trough level quantitation for evaluation of patients with loss of response to adalimumab

**Interpretation:** Currently, adalimumab quantitation is one of the most commonly tested monoclonal antibodies in routine practice; this testing is generally performed in conjunction with immunogenicity assessment for antibodies to adalimumab (ATA). Most often, this testing is ordered for patients with inflammatory bowel disease (IBD) who are on adalimumab therapy and who are experiencing loss of response, but the testing may be ordered for anyone on adalimumab. Results from adalimumab and ATA testing play an important role in patient management. When measured at trough, for patients who have undetectable or low concentrations of adalimumab, but no detectable ATA, the physician may choose to increase the dose of adalimumab in an attempt to increase the amount of the drug in circulation. If the patient has low adalimumab in the presence of an ATA, in many cases the physician may switch the patient to another tumor necrosis factor (TNF) inhibitor. In contrast, for patients with increased trough concentrations of adalimumab, whether or not an ATA is present, it may be necessary to switch the patient to a therapy with a different mechanism of action, such as the anti-alpha4-beta-7-integrin antibody vedolizumab or the IL12/IL23 antibody ustekinumab, in the setting of IBD. Adalimumab quantitation will be interpreted in 2 different ways. When measured at trough, individuals may be considered to have adequate trough levels when drug concentrations are above 5 mcg/mL, and faster clearance of the drug, which may warrant a dosing adjustment or additional action if adalimumab trough concentration is below or equal to 5 mcg/mL. Adalimumab quantitation may influence patient management decisions as to whether therapy should continue as is, dose escalation is necessary, or a switch to a new therapeutic regimen is needed. Low trough concentrations may be correlated with loss of response to adalimumab. For adalimumab trough concentrations of 5.0 mcg/mL or less, testing for antibodies to ATA is suggested. For adalimumab trough concentrations above 5.0 mcg/mL, the presence of ATA is unlikely; patients experiencing loss of response to adalimumab may benefit from an increased dose or more frequent dosing. Adalimumab concentration results above 35 mcg/mL are suggestive of a blood draw at a time-point in treatment other than trough.

**Reference Values:**
ADALX: Limit of quantitation is 0.8 mcg/mL. Optimal therapeutic ranges are disease specific.

ADLAB: <14.0 AU/mL

**Clinical References:**
rarely be congenital (Upshaw-Shulman syndrome), but far more commonly is acquired. Acquired TTP may be considered to be primary or idiopathic (the most frequent type) or associated with distinctive clinical conditions (secondary TTP) such as medications, hematopoietic stem cell or solid organ transplantation, sepsis, and malignancy. The isolation and characterization of an IgG autoantibody frequently found in patients with idiopathic TTP, clarified the basis of this entity and led to the isolation and characterization of a metalloprotease called ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif 13 repeats), which is the target for the IgG autoantibody, leading to a functional deficiency of ADAMTS13. ADAMTS13 cleaves the ultra high-molecular-weight multimers of von Willebrand factor (VWF) at the peptide bond Tyr1605-Met1606 to disrupt VWF-induced platelet aggregation. The IgG antibody prevents this cleavage and leads to TTP. Although the diagnosis of TTP may be confirmed with ADAMTS13 activity and inhibition studies, the decision to initiate plasma exchange should not be delayed pending results of this assay.

**Useful For:** Assisting with the diagnosis of congenital or acquired thrombotic thrombocytopenic purpura

**Interpretation:** Less than 10% ADAMTS13 activity is highly indicative of thrombotic thrombocytopenic purpura (TTP) in an appropriate clinical setting. The presence of ADAMTS13 inhibition (positive inhibitor screen) with a measurable antibody titer is most consistent with an acquired TTP.

**Reference Values:**

**ADAMTS13 ACTIVITY ASSAY**

> or =70%

**ADAMTS13 INHIBITOR SCREEN**

Negative

**ADAMTS13 BETHESDA TITER**

<0.4 BU

**Clinical References:**


---

**ADAMBU**

**ADAMTS13 Inhibitor Bethesda Titer**

**Clinical Information:** Thrombotic thrombocytopenic purpura (TTP), a rare (estimated incidence of 3.7 cases per million) and potentially fatal thrombotic microangiopathy (TMA) syndrome, is characterized by a pentad of symptoms: thrombocytopenia, microangiopathic hemolytic anemia (intravascular hemolysis and presence of peripheral blood schistocytes), neurological symptoms, fever, and renal dysfunction. The large majority of patients initially present with thrombocytopenia and peripheral blood evidence of microangiopathy, and in the absence of any other potential explanation for such findings, satisfy criteria for early initiation of plasma exchange, which is critical for patient survival. TTP may rarely be congenital (Upshaw-Shulman syndrome), but far more commonly is acquired. Acquired TTP may be considered to be primary or idiopathic (the most frequent type) or associated with distinctive clinical conditions (secondary TTP) such as medications, hematopoietic stem cell or solid organ transplantation, sepsis, and malignancy. The isolation and characterization of an IgG autoantibody frequently found in patients with idiopathic TTP, clarified the basis of this entity and led to the isolation and characterization of a metalloprotease called ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif 13 repeats), which is the target for the IgG autoantibody, leading to a functional deficiency of ADAMTS13. ADAMTS13 cleaves the ultra-high-molecular-weight multimers of von Willebrand factor (VWF) at the peptide bond Tyr1605-Met1606 to disrupt VWF-induced platelet aggregation. The IgG antibody prevents this cleavage and leads to TTP. Although the diagnosis of TTP may be confirmed with ADAMTS13 activity and inhibition studies, the decision to initiate plasma exchange should not be delayed pending results of
Useful For: Assisting with the diagnosis of congenital or acquired thrombotic thrombocytopenic purpura

Interpretation: Less than 10% ADAMTS13 activity is highly indicative of thrombotic thrombocytopenic purpura (TTP) in an appropriate clinical setting. The presence of ADAMTS13 inhibition (positive inhibitor screen) with a measurable antibody titer is most consistent with an acquired TTP.

Reference Values:
<0.4 BU

Only orderable as part of a profile. For more information see ADM13 / ADAMTS13 Activity and Inhibitor Profile.


<table>
<thead>
<tr>
<th>Code</th>
<th>Test Description</th>
<th>Reference Values</th>
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<tbody>
<tr>
<td>ADSTM</td>
<td>Additional Flow Stimulant (Bill Only)</td>
<td>This test is for billing purposes only.</td>
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<td>62206</td>
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<td>This is not an orderable test.</td>
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<tr>
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<td>This test is for billing purposes only.</td>
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<tr>
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<tr>
<td>MGSTM</td>
<td>Additional Flow Stimulant, LPMGF (Bill Only)</td>
<td>This test is for billing purposes only.</td>
</tr>
<tr>
<td>62207</td>
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<td>This is not an orderable test.</td>
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<tr>
<td>FADDB</td>
<td>Adenosine Deaminase, Blood</td>
<td>0.3 - 1.4 IU/g Hb</td>
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<tr>
<td>57876</td>
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<td></td>
</tr>
<tr>
<td>FADDC</td>
<td>Adenosine Deaminase, CSF</td>
<td>0.0 – 1.5 U/L</td>
</tr>
<tr>
<td>58029</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FADPC</td>
<td>Adenosine Deaminase, Pericardial Fluid</td>
<td>0.0-11.3 U/L</td>
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<tr>
<td>75004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FADPT</td>
<td>Adenosine Deaminase, Peritoneal Fluid</td>
<td>0.0 – 7.3 U/L</td>
</tr>
<tr>
<td>75003</td>
<td></td>
<td></td>
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<tr>
<td>FADPL</td>
<td>Adenosine Deaminase, Pleural Fluid</td>
<td>0.0-9.4 U/L</td>
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<tr>
<td>75002</td>
<td></td>
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</tr>
</tbody>
</table>
**Adenovirus DNA, Quantitative Real-Time PCR**

**Reference Values:**
REFERENCE RANGE: <500 copies/mL

---

**Adenovirus Immunostain, Technical Component Only**

**Clinical Information:** Adenoviruses are 65 to 80 nm, nonenveloped, regular icosahedron pathogens containing double-stranded DNA. Adenovirus infection is often associated with respiratory (HAdV-B and C) and gastrointestinal illness (HAdV-F serotypes 40 and 41) as well as conjunctivitis (HAdV-B and D). Over 51 types of immunologically distinct adenovirus serotypes have been categorized.

**Useful For:** Identification of adenovirus infection

**Interpretation:** The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**Adenovirus, Molecular Detection, PCR**

**Clinical Information:** Human adenoviruses cause a variety of diseases including pneumonia, cystitis, conjunctivitis, diarrhea, hepatitis, myocarditis, and encephalitis. In humans, adenoviruses have been recovered from almost every organ system. Infections can occur at any time of the year and in all age groups. Currently, there are 51 adenovirus serotypes that have been grouped into 6 separate subgenera. Culture is the gold standard for the diagnosis for adenovirus infection. However, it can take up to 3 weeks to achieve culture results (Mayo Clinic's shell vial culture provides more rapid results, reported at 2 and 5 days). Serological tests have faster turnaround times, but can be less sensitive compared to culture. PCR offers a rapid, specific, and sensitive means of diagnosis by detecting adenovirus DNA.

**Useful For:** Aiding in the diagnosis of adenovirus infections

**Interpretation:** A positive result indicates the presence of adenoviruses. A negative result does not rule out the presence of adenoviruses because organisms may be present at levels below the detection limits of this assay.

**Reference Values:**
Negative

**Clinical References:**
Adenovirus, Molecular Detection, PCR, Plasma

Clinical Information: Human adenoviruses cause a variety of diseases including pneumonia, cystitis, conjunctivitis, diarrhea, hepatitis, myocarditis, and encephalitis. In humans, adenoviruses have been recovered from almost every organ system. Infections can occur at any time of the year and in all age groups. Currently, there are 51 adenovirus serotypes that have been grouped into 6 separate subgenera. Culture is the gold standard for the diagnosis of adenovirus infection; however, it can take up to 3 weeks to achieve culture results. Mayo's shell vial culture provides more rapid results, reported at 2 and 5 days. While PCR offers a rapid, specific, and sensitive means of diagnosis by detecting adenovirus DNA.

Useful For: An aid in diagnosing adenovirus infections

Interpretation: A positive result indicates the presence of adenovirus nucleic acid. A negative result does not rule out the presence of adenoviruses because organisms may be present at levels below the detection limits of this assay.

Reference Values:
Negative

Clinical References:

Adiponectin

Reference Values:
Reference Ranges for Adiponectin:

<table>
<thead>
<tr>
<th>Body Mass Index</th>
<th>Males (mcg/mL)</th>
<th>Females (mcg/mL)</th>
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<tbody>
<tr>
<td>&lt;25 kg/meters-squared</td>
<td>4-26</td>
<td>5-37</td>
</tr>
<tr>
<td>25-30 kg/meters-squared</td>
<td>4-20</td>
<td>5-28</td>
</tr>
<tr>
<td>&gt;30 kg/meters-squared</td>
<td>2-20</td>
<td>4-22</td>
</tr>
</tbody>
</table>

ADmark Phospho-Tau/Total-Tau/A Beta 42, Analysis & Interp, CSF (Symptomatic)

Reference Values:
A final report will be attached in MayoAccess.

Adrenocorticotropic Hormone, ACTH, IgE
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<tbody>
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</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

Adrenocorticotropic Hormone (ACTH), Plasma

**Clinical Information:** Adrenocorticotropic hormone (ACTH) is synthesized by the pituitary in response to corticotropin-releasing hormone (CRH), which is released by the hypothalamus. ACTH stimulates adrenal cortisol production. Plasma ACTH and cortisol levels exhibit peaks (6-8 a.m.) and nadirs (11 p.m.). Disorders of cortisol production that might affect circulating ACTH concentrations include: Hypercortisolism - Cushing syndrome: - Cushing disease (pituitary ACTH-producing tumor) - Ectopic ACTH-producing tumor - Ectopic CRH - Adrenal cortisol-producing tumor - Adrenal hyperplasia (non-ACTH dependent, autonomous cortisol-producing adrenal nodules) Hypocortisolism - Addison disease-primary adrenal insufficiency - Secondary adrenal insufficiency - Pituitary insufficiency - Hypothalamic insufficiency - Congenital adrenal hyperplasia-defects in enzymes involved in cortisol synthesis

**Useful For:** Determining the cause of hypercortisolism and hypocortisolism

**Interpretation:** In a patient with hypocortisolism, an elevated adrenocorticotropic hormone (ACTH) indicates primary adrenal insufficiency, whereas a value that is not elevated is consistent with secondary adrenal insufficiency from a pituitary or hypothalamic cause. In a patient with hypercortisolism (Cushing syndrome), a suppressed value is consistent with a cortisol-producing adrenal adenoma or carcinoma, primary adrenal micronodular hyperplasia, or exogenous corticosteroid use. Normal or elevated ACTH in a patient with Cushing syndrome puts the patient in the ACTH-dependent Cushing syndrome category. This is due to either an ACTH-producing pituitary adenoma or ectopic production of ACTH (bronchial carcinoid, small cell lung cancer, others). Further diagnostic studies such as dexamethasone suppression testing, corticotropin-releasing hormone stimulation testing, petrosal sinus sampling, and imaging studies are usually necessary to define the ACTH source. ACTH concentrations vary considerably depending on physiological conditions. Therefore, ACTH results should always be evaluated with simultaneously measured cortisol concentrations.

**Reference Values:**
- 7.2-63 pg/mL (a.m. draws)
- No established reference values for p.m. draws
- Pediatric reference values are the same as adults, as confirmed by peer reviewed literature.


For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.


Adulterants Survey, Chain of Custody, Urine

**Clinical Information:** Specimen adulteration is the manipulation of a sample that may cause falsely negative test results for the presence of drugs of abuse. Common adulterants that may affect testing are water, soap, bleach, vinegar, oxidants, and salt. The adulteration testing includes assessment of
creatinine concentration, pH, urine specific gravity, presence or absence of an oxidant, and presence or absence of nitrite. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Useful For:** Assess the possible adulteration of a urine specimen submitted for drug of abuse testing, as well as for providing the urine creatinine for "creatinine normalization" This chain-of-custody test is intended to be used in a setting where the test results can be used definitively to make a diagnosis.

**Interpretation:** See Adulterant Survey Algorithm in Special Instructions.

**Reference Values:**

Cutoff concentrations
- Oxidants: 200 mg/L
- Nitrites: 500 mg/L

**Clinical References:**

### ADULT 29345

**Adulterants Survey, Urine**

**Clinical Information:** Specimen adulteration is the manipulation of a sample that may cause falsely negative test results for the presence of drugs of abuse. Common adulterants that may affect testing are water, soap, bleach, vinegar, oxidants, and salt. The adulteration testing includes assessment of creatinine concentration, pH, urine specific gravity, presence or absence of an oxidant, and presence or absence of nitrite.

**Useful For:** Assess the possible adulteration of a urine specimen submitted for drug of abuse testing, as well as for providing the urine creatinine for "creatinine normalization"

**Interpretation:** See Adulterant Survey Algorithm in Special Instructions.

**Reference Values:**

Cutoff concentrations
- Oxidants: 200 mg/L
- Nitrites: 500 mg/L

### ISAE 45246

**Aerobe Identification by Sequencing (Bill Only)**

**Reference Values:**

This test is for billing purposes only. This is not an orderable test.

### AGXTZ 35348

**AGXT Gene, Full Gene Analysis**

**Clinical Information:** Primary hyperoxaluria type 1 (PH1) is a hereditary disorder of glyoxylate metabolism caused by deficiency of alanine:glyoxylate-aminotransferase (AGT), a hepatic enzyme that converts glyoxylate to glycine. Absence of AGT activity results in conversion of glyoxylate to oxalate, which is not capable of being degraded. Therefore, excess oxalate is excreted in the urine, causing kidney stones (urolithiasis), nephrocalcinosis, and kidney failure. As kidney function declines, blood levels of
oxalate increase markedly, and oxalate combines with calcium to form calcium oxalate deposits in the kidney, eyes, heart, bones, and other organs, resulting in systemic disease. Pyridoxine (vitamin B6), a cofactor of AGT, is effective in reducing urine oxalate excretion in some PH1 patients. Presenting symptoms of PH1 include nephrolithiasis, nephrocalcinosis, or end-stage kidney disease with or without a history of urolithiasis. Age of symptom onset is variable; however, most individuals present in childhood or adolescence with symptoms related to kidney stones. In some infants with a more severe phenotype, kidney failure may be the initial presenting feature. Less frequently, affected individuals present in adulthood with recurrent kidney stones or kidney failure. End-stage kidney disease is most often seen in the third decade of life, but can occur at any age. The exact prevalence and incidence of PH1 are not known, but prevalence rates of 1 to 3 per million population and incidences of 0.1 per million/year have been estimated from population surveys. Biochemical testing is indicated in patients with possible primary hyperoxaluria. Measurement of urinary oxalate is strongly preferred, with correction to adult body surface area in pediatric patients (HYOX / Hyperoxaluria Panel, Urine; OXU / Oxalate, 24 Hour, Urine). Abnormal urinary excretion of oxalate is strongly suggestive of, but not diagnostic for, this disorder, as there are other forms of inherited (type 2 and non-PH1/PH2) hyperoxaluria and secondary hyperoxaluria that may result in similarly elevated urine oxalate excretion rates. An elevated urine glycolate in the presence of hyperoxaluria is suggestive of PH1. Historically, the diagnosis of PH1 was confirmed by AGT enzyme analysis performed on liver biopsy; however, this has been replaced by molecular testing, which forms the basis of confirmatory or carrier testing in most cases. PH1 is inherited as an autosomal recessive disorder caused by mutations in the AGXT gene, which encodes the enzyme AGT. Several common AGXT mutations have been identified including c.33dupC, p.Gly170Arg (c.508G->A), and p.Ile244Thr (c.731T->C). These mutations account for at least 1 of the 2 affected alleles in approximately 70% of individuals with PH1. Direct sequencing of the AGXT gene is predicted to identify 99% of alleles in individuals who are known by enzyme analysis to be affected with PH1. While age of onset and severity of disease is variable and not necessarily predictable by genotype, a correlation between pyridoxine responsiveness and homozygosity for the p.Gly170Arg mutation has been observed. (Note: testing for the p.Gly170Arg mutation only is available by ordering AGXTG / Alanine:Glyoxylate Aminotransferase [AGXT] Mutation Analysis [G170R], Blood). Pyridoxine (vitamin B6) is a known cofactor of AGT and is effective in reducing urine oxalate excretion in some PH1 patients treated with pharmacologic doses. Individuals with 2 copies of the p.Gly170Arg mutation have been shown to normalize their urine oxalate when treated with pharmacologic doses of pyridoxine and those with a single copy of the mutation show reduction in urine oxalate. This is valuable because not all patients have been shown to be responsive to pyridoxine, and strategies that help to identify the individuals most likely to benefit from such targeted therapies are desirable.

Useful For: Confirming a diagnosis of primary hyperoxaluria type 1 Carrier testing for individuals with a family history of primary hyperoxaluria type 1 in the absence of known mutations in the family

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.

Alanine Aminotransferase (ALT) (GPT), Serum

Clinical Information: Alanine aminotransferase (ALT) is present primarily in liver cells. In viral hepatitis and other forms of liver disease associated with hepatic necrosis, serum ALT is elevated even before the clinical signs and symptoms of the disease appear. Although serum levels of both aspartate aminotransferase (AST) and ALT become elevated whenever disease processes affect liver cell integrity, ALT is a more liver-specific enzyme. Serum elevations of ALT are rarely observed in conditions other than parenchymal liver disease. Moreover, the elevation of ALT activity persists longer than does AST activity.

Useful For: Diagnosis and monitoring of liver disease associated with hepatic necrosis

Interpretation: Elevated alanine aminotransferase (ALT) values are seen in parenchymal liver diseases characterized by a destruction of hepatocytes. Values are typically at least 10 times above the normal range. Levels may reach values as high as 100 times the upper reference limit, although 20- to 50-fold elevations are most frequently encountered. In infectious hepatitis and other inflammatory conditions affecting the liver, ALT is characteristically as high as or higher than aspartate aminotransferase (AST), and the ALT:AST ratio, which normally and in other condition is less than 1, becomes greater than unity. ALT levels are usually elevated before clinical signs and symptoms of disease appear.

Reference Values:
Males
> or =1 year: 7-55 U/L
Reference values have not been established for patients who are <12 months of age.
Females
> or =1 year: 7-45 U/L
Reference values have not been established for patients who are <12 months of age.


Alanine:Glyoxylate Aminotransferase (AGXT) Mutation Analysis (G170R), Blood

Clinical Information: Primary hyperoxaluric type 1 (PH1) is an autosomal recessive disorder in which excessive oxalates are formed by the liver and excreted by the kidneys, causing a wide spectrum of disease ranging from renal failure in infancy to mere renal stones in late adulthood. It is caused by deficiencies of the liver-specific peroxisomal enzyme AGXT (alanine-glyoxylate amino-transferase). The diagnosis may be suspected when clinical signs, increased urinary oxalate, glycolate, and glycerate excretion are present. Diagnostic confirmation requires the enzyme assay of the liver tissue, although this test is not readily available. The toxicity of excess oxalate has been implicated in disease pathogenesis. Thus, treatment options have primarily centered on limiting oxalate ingestion and absorption. Pyridoxine (vitamin B[6]) has proven to be a promising therapeutic agent by increasing the concentration of cofactor involved in the metabolic reactions that decrease oxalate production. However, only 20% to 30% of patients have been known to be responsive to pyridoxine. Testing patients for pyridoxine responsiveness has been recommended at any stage of renal function, although assessment of pyridoxine responsiveness is not always easy to perform and diagnostic criteria have not been standardized. Recently, researchers at Mayo Clinic found that patients with a particular mutation (Gly170Arg) in the AGXT gene are responsive to the pyridoxine, while affected individuals without this mutation are not responsive.

Useful For: Identifying patients with the pyridoxine responsive form of primary hyperoxaluria type 1 (PH1) Determining the presence of the Gly170Arg (G170R) mutation in the AGXT gene Carrier testing of at-risk family members
Interpretation: Reported as negative or positive. The laboratory provides an interpretation of the results. This interpretation includes an overview of the results and their significance and a correlation to available clinical information.

Reference Values:
An interpretive report will be provided.


FALUF 57286 Albumin, Body Fluid
Reference Values:
Units: mg/dL
Not Established

ALB 8436 Albumin, Serum
Clinical Information: Albumin is a carbohydrate-free protein, which constitutes 55% to 65% of total plasma protein. It maintains oncotic plasma pressure, is involved in the transport and storage of a wide variety of ligands, and is a source of endogenous amino acids. Albumin binds and solubilizes various compounds, including bilirubin, calcium, long-chain fatty acids, toxic heavy metal ions, and numerous pharmaceuticals. Hypoalbuminemia is caused by several factors: impaired synthesis due either to liver disease (primary) or due to diminished protein intake (secondary), increased catabolism as a result of tissue damage and inflammation, malabsorption of amino acids, and increased renal excretion (eg, nephrotic syndrome).

Useful For: Assessing nutritional status

Interpretation: Hyperalbuminemia is of little diagnostic significance except in the case of dehydration. When plasma or serum albumin values fall below 2.0 g/dL, edema is usually present.

Reference Values:
> or =12 months: 3.5-5.0 g/dL

Reference values have not been established for patients who are <12 months of age.

For SI unit Reference Values, see


FALBU 90309 Albuterol, Serum/Plasma
Reference Values:
Reporting limit determined each analysis

Synonym(s): Proventil

Peak plasma levels following a 180 mcg dose via an
inhaler: 1.5 ng/mL at 13 minutes post dose.

Peak plasma levels following inhalation of a cumulative dose of 1 mg and 4 mg: approximately 5 and 20 ng/mL, respectively, 5 minutes post dose.

Peak plasma levels following a single 8 mg oral-sustained release tablet:
13 ng/mL at 5.0 hours post dose.

Average steady-state peak and trough plasma levels following a 4 mg (normal release tablet) every 6 hours for 5 days: 15 and 9.9 ng/mL, respectively.

Serum/plasma concentrations may vary significantly depending on dose, formulation, route of administration, device, lung function, and user mechanics.

**FABI 57729**

**Alcohol Biomarkers, Urine**

**Reference Values:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Screening Threshold</th>
<th>Confirmation Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl glucuronide</td>
<td>500 ng/mL</td>
<td>500 ng/mL</td>
</tr>
<tr>
<td>Ethyl sulfate</td>
<td>250 ng/mL</td>
<td>Alternative explanations should be explored for any positive finding.</td>
</tr>
</tbody>
</table>

**Clinical References:** Samhsa Advisory, Spring 2012 Volume 11, Issue 2

**ALS 8363**

**Aldolase, Serum**

**Clinical Information:** Aldolase is necessary for glycolysis in muscle as a "rapid response" pathway for production of adenosine triphosphate, independent of tissue oxygen. Aldolase catalyses the conversion of fructose 1,6-diphosphate into dihydroxyacetone phosphate and glyceraldehyde 3-phosphate, an important reaction in the glycolytic breakdown of glucose to lactate in muscle. Aldolase is a tetramer whose primary structure depends upon the tissue from which it was synthesized (liver, muscle, brain). The brain form of aldolase has, because of its preponderance in white cells, been suggested to be a leukemia marker, but this is not confirmed. Elevated values are found in muscle diseases, such as Duchenne muscular dystrophy, dermatomyositis, polymyositis, and limb-girdle dystrophy.

**Useful For:** Detection of muscle disease

**Interpretation:** The highest levels of aldolase are found in progressive (Duchenne) muscular dystrophy. Lesser elevations are found in dermatomyositis, polymyositis, and limb-girdle dystrophy. In dystrophic conditions causing hyperaldolosemia, the increase in aldolase becomes less dramatic as muscle mass decreases. Reference (normal) values are observed in polio, myasthenia gravis, and multiple sclerosis. Aldolase increases in myocardial infarction in a time pattern similar to the aspartate aminotransferase. Increases are also associated with acute viral hepatitis, but levels are normal or slightly elevated in chronic hepatitis, portal cirrhosis, and obstructive jaundice. Elevations may also be seen with gangrene, prostate tumors, trichinosis, some carcinomas metastatic to the liver, some chronic leukemias, some blood dyscrasias, and delirium tremens.

**Reference Values:**

0-16 years: <14.5 U/L
Aldosterone with Sodium, 24 Hour, Urine

Clinical Information: Aldosterone stimulates sodium transport across cell membranes, particularly in the distal renal tubule where sodium is exchanged for hydrogen and potassium. Secondarily, aldosterone is important in the maintenance of blood pressure and blood volume. Aldosterone is the major mineralocorticoid and is produced by the adrenal cortex. The renin-angiotensin system is the primary regulator of the synthesis and secretion of aldosterone. Likewise, increased concentrations of potassium in the plasma may directly stimulate adrenal production of the hormone. Under physiologic conditions, pituitary adrenocorticotropic hormone can stimulate aldosterone secretion. Urinary aldosterone levels are inversely correlated with urinary sodium excretion. Normal subjects will show a suppression of urinary aldosterone with adequate sodium repletion. Primary hyperaldosteronism, which may be caused by aldosterone-secreting adrenal adenoma/carcinomas or adrenal cortical hyperplasia, is characterized by hypertension accompanied by increased aldosterone levels, hypernatremia, and hypokalemia. Secondary hyperaldosteronism (eg, in response to renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartterâ€™s syndrome) is characterized by increased aldosterone levels and increased plasma rennin activity.

Useful For: Investigation of primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) and secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome)

Interpretation: Under normal circumstances, if the 24-hour urinary sodium excretion is >200 mEq, the urinary aldosterone excretion should be <10 mcg/24 hours. Urinary aldosterone excretion >12 mcg/24 hours as part of an aldosterone suppression test is consistent with hyperaldosteronism. 24-Hour urinary sodium excretion should exceed 200 mEq to document adequate sodium repletion. See Renin-Aldosterone Studies in Special Instructions. Note: Advice on stimulation or suppression tests is available from Mayo Clinic’s Division of Endocrinology and may be obtained by calling Mayo Medical Laboratories.

Reference Values:
ALDOSTERONE
- 0-30 days: 0.7-11.0 mcg/24 hours*
- 1-11 months: 0.7-22.0 mcg/24 hours*
- > or =1 year: 2.0-20.0 mcg/24 hours*


SODIUM
- 41-227 mmol/24 hours
  - If the 24-hour urinary sodium excretion is >200 mmol, the urinary aldosterone excretion should be <10 mcg.


Aldosterone, 24 Hour, Urine

Clinical Information: Aldosterone stimulates sodium transport across cell membranes, particularly in the distal renal tubule where sodium is exchanged for hydrogen and potassium. Secondarily, aldosterone is important in the maintenance of blood pressure and blood volume. Aldosterone is the major mineralocorticoid and is produced by the adrenal cortex. The renin-angiotensin system is the primary regulator of the synthesis and secretion of aldosterone. Likewise, increased concentrations of potassium in the plasma may directly stimulate adrenal production of the hormone. Under physiologic...
conditions, pituitary adrenocorticotropic hormone can stimulate aldosterone secretion. Urinary aldosterone levels are inversely correlated with urinary sodium excretion. Normal subjects will show a suppression of urinary aldosterone with adequate sodium repletion. Primary hyperaldosteronism, which may be caused by aldosterone-secreting adrenal adenoma/carcinomas or adrenal cortical hyperplasia, is characterized by hypertension accompanied by increased aldosterone levels, hypernatremia, and hypokalemia. Secondary hyperaldosteronism (eg, in response to renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter’s syndrome) is characterized by increased aldosterone levels and increased plasma rennin activity.

**Useful For:** Investigation of primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) and secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome)

**Interpretation:** Under normal circumstances, if the 24-hour urinary sodium excretion is greater than 200 mEq, the urinary aldosterone excretion should be less than 10 mcg/24 hours. Urinary aldosterone excretion greater than 12 mcg/24 hours as part of an aldosterone suppression test is consistent with hyperaldosteronism. 24-Hour urinary sodium excretion should exceed 200 mEq to document adequate sodium repletion. See Renin-Aldosterone Studies in Special Instructions. Note: Advice on stimulation or suppression tests is available from Mayo Clinic’s Division of Endocrinology and may be obtained by calling Mayo Medical Laboratories.

**Reference Values:**
- 0-30 days: 0.7-11.0 mcg/24 hours*
- 31 days-11 months: 0.7-22.0 mcg/24 hours*
- > or =1 year: 2.0-20.0 mcg/24 hours


For SI unit Reference Values, see [https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html](https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html).

**Clinical References:**
Endocrinology and may be obtained by calling Mayo Medical Laboratories.

**Reference Values:**
No established reference values.

**Clinical References:**

**ALAV 6349**

**Aldosterone, Left Adrenal Vein, Serum**

**Clinical Information:**
Aldosterone stimulates sodium transport across cell membranes, particularly in the distal renal tubule where sodium is exchanged for hydrogen and potassium. Secondarily, aldosterone is important in the maintenance of blood pressure and blood volume. Aldosterone is the major mineralocorticoid and is produced by the adrenal cortex. The renin-angiotensin system is the primary regulator of the synthesis and secretion of aldosterone. Likewise, increased concentrations of potassium in the plasma may directly stimulate adrenal production of the hormone. Under physiologic conditions, pituitary adrenocorticotropic hormone is not a major factor in regulating aldosterone secretion. See Steroid Pathways in Special Instructions.

**Useful For:**
Investigation of primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) and secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome)

**Interpretation:**
A high ratio of serum aldosterone (SA) in ng/dL to plasma renin activity (PRA) in ng/mL per hour, is a positive screening test result, a finding that warrants further testing. An SA/PRA ratio > 20 is only interpretable with an SA > or =15 ng/dL and indicates probable primary aldosteronism. Renal disease, such as unilateral renal artery stenosis, results in elevated renin and aldosterone levels. Renal venous catheterization may be helpful. A positive test is a renal venous renin ratio (affected/normal) >1.5. See Renin-Aldosterone Studies and Steroid Pathways in Special Instructions. Note: Advice on stimulation or suppression tests is available from Mayo Clinic's Division of Endocrinology and may be obtained by calling Mayo Medical Laboratories.

**Reference Values:**
No established reference values.

**Clinical References:**

**ARAV 6348**

**Aldosterone, Right Adrenal Vein, Serum**

**Clinical Information:**
Aldosterone stimulates sodium transport across cell membranes, particularly in the distal renal tubule where sodium is exchanged for hydrogen and potassium. Secondarily, aldosterone is important in the maintenance of blood pressure and blood volume. Aldosterone is the major mineralocorticoid and is produced by the adrenal cortex. The renin-angiotensin system is the primary regulator of the synthesis and secretion of aldosterone. Likewise, increased concentrations of potassium in the plasma may directly stimulate adrenal production of the hormone. Under physiologic conditions, pituitary adrenocorticotropic hormone is not a major factor in regulating aldosterone secretion. See Steroid Pathways in Special Instructions.

**Useful For:**
Investigation of primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) and secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome)
**Interpretation:** A high ratio of serum aldosterone (SA) in ng/dL to plasma renin activity (PRA) in ng/mL per hour, is a positive screening test result, a finding that warrants further testing. An SA/PRA ratio > or =20 is only interpretable with an SA > or =15 ng/dL and indicates probable primary aldosteronism. Renal disease, such as unilateral renal artery stenosis, results in elevated renin and aldosterone levels. Renal venous catheterization may be helpful. A positive test is a renal venous renin ratio (affected/normal) >1.5. See Renin-Aldosterone Studies and Steroid Pathways in Special Instructions. Note: Advice on stimulation or suppression tests is available from Mayo Clinic's Division of Endocrinology and may be obtained by calling Mayo Medical Laboratories.

**Reference Values:**
No established reference values.

**Clinical References:**

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**Aldosterone, Serum**

**Clinical Information:** Aldosterone stimulates sodium transport across cell membranes, particularly in the distal renal tubule where sodium is exchanged for hydrogen and potassium. Secondarily, aldosterone is important in the maintenance of blood pressure and blood volume. Aldosterone is the major mineralocorticoid and is produced by the adrenal cortex. The renin-angiotensin system is the primary regulator of the synthesis and secretion of aldosterone. Likewise, increased concentrations of potassium in the plasma may directly stimulate adrenal production of the hormone. Under physiologic conditions, pituitary adrenocorticotropic hormone is not a major factor in regulating aldosterone secretion. See Steroid Pathways in Special Instructions.

**Useful For:** Investigation of primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) and secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome)

**Interpretation:** A high ratio of serum aldosterone (SA) in ng/dL to plasma renin activity (PRA) in ng/mL per hour, is a positive screening test result, a finding that warrants further testing. An SA/PRA ratio > or =20 is only interpretable with an SA > or =15 ng/dL and indicates probable primary aldosteronism. Renal disease, such as unilateral renal artery stenosis, results in elevated renin and aldosterone levels. Renal venous catheterization may be helpful. A positive test is a renal venous renin ratio (affected/normal) >1.5. See Renin-Aldosterone Studies and Steroid Pathways in Special Instructions. Note: Advice on stimulation or suppression tests is available from Mayo Clinic's Division of Endocrinology and may be obtained by calling Mayo Medical Laboratories.

**Reference Values:**
0-30 days: 17-154 ng/dL*
31 days-11 months: 6.5-86 ng/dL*
1-10 years:
< or =40 ng/dL (supine)*
< or =124 ng/dL (upright)*
> or =11 years: < or =21 ng/dL (a.m. peripheral vein specimen)


For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.

**Clinical References:**

**FALPE**

**Alfalfa (Medicago sativa) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal/Borderline 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 High Positive 4 17.50-49.99 Very High Positive 5 50.0-99.99 Very High Positive Very High Positive >99.99 Very High Positive

**Reference Values:**

<0.35 kU/L

**FALKC**

**ALK on Cytology Specimens, FISH**

**Clinical Information:** Lung cancer is the leading cause of cancer death in the United States. Non-small cell lung carcinoma (NSCLC) accounts for 75% to 80% of all lung cancers with an overall 5-year survival rate of 10% to 15%. Standard chemotherapy regimens have had marginal success in improving clinical outcomes. Rearrangements of the anaplastic lymphoma receptor tyrosine kinase (ALK) locus are found in a small subset of lung carcinomas and the identification of ALK-driven lung cancer guides important therapeutic management of these tumors. Rearrangement (translocation) of the ALK gene with a fusion partner gene, most commonly echinoderm microtubule-associated protein-like 4 (EML4), results in a constitutively active fusion gene. Lung cancers harboring ALK rearrangements are highly sensitive to ALK inhibitor drugs, which work by blocking certain kinases including those produced by the abnormal ALK fusion gene. The FDA has approved the use of Xalkori (Crizotinib), an ALK inhibitor drug, for NSCLC patients with tumors exhibiting ALK rearrangements. The FDA-approved companion diagnostic assay for the detection of the ALK gene rearrangements is a FISH test that utilizes the Vysis ALK break apart FISH probe kit and is approved for formalin-fixed, paraffin-embedded (FFPE) material only. Unfortunately, not all NSCLC patients have sufficient FFPE material for ALK testing.

**Useful For:** Detection of rearrangements involving the ALK gene region at 2p23 in patients with non-small cell lung carcinoma who may benefit from treatment with the ALK inhibitor drugs, like Xalkori (Crizotinib), on previously stained routine cytology slides

**Interpretation:** An interpretive report will be provided.

**Reference Values:**

An interpretative report will be provided.


**ALP**

**Alkaline Phosphatase, Serum**

**Clinical Information:** Alkaline phosphatase in serum consists of 4 structural genotypes: the liver-bone-kidney type, the intestinal type, the placental type, and the variant from the germ cells. It occurs in osteoblasts, hepatocytes, leukocytes, the kidneys, spleen, placenta, prostate, and the small
intestine. The liver-bone-kidney type is particularly important. A rise in the alkaline phosphatase occurs with all forms of cholestasis, particularly with obstructive jaundice. It is also elevated in diseases of the skeletal system, such as Paget disease, hyperparathyroidism, rickets and osteomalacia, as well as with fractures and malignant tumors. A considerable rise in the alkaline phosphatase activity is sometimes seen in children and juveniles. It is caused by increased osteoblast activity following accelerated bone growth.

**Useful For:** Diagnosing and monitoring treatment of liver, bone, intestinal, and parathyroid diseases

**Interpretation:** Increases in serum alkaline phosphatase (ALP) activity commonly originate from 1 or both of 2 sources: liver and bone. Consequently, serum ALP measurements are of particular interest in the investigation of 2 groups of conditions: hepatobiliary disease and bone disease associated with increased osteoblastic activity. Serum ALP was the first enzyme to be used for the investigation of hepatic disease. The response of the liver to any form of biliary tree obstruction induces the synthesis of ALP by hepatocytes. The newly formed coenzyme is released from the cell membrane by the action of bile salts and enters the circulation to increase the enzyme activity in serum. Increase tends to be more notable (greater than 4-fold the upper reference value [URV]) in extrahepatic obstruction (eg, by stone, by cancer of the head of the pancreas) than in intrahepatic obstruction, and is greater the more complete the obstruction. Serum enzyme activities may reach 10 to 12 times the URV and usually return to baseline on surgical removal of the obstruction. A similar increase is seen in patients with advanced primary liver cancer or widespread secondary hepatic metastases. ALP increase (greater than 2-fold the URV) can predict transplant-free survival rates of patients with primary biliary cirrhosis. Liver diseases that principally affect parenchymal cells, such as infectious hepatitis, typically show only moderately (less than 3-fold) increased or even normal serum ALP activities. Increases may also be seen as a consequence of a reaction to drug therapy, and ALT/ALP-based criteria to discriminate the type of liver injury in drug-induced hepatic toxicity have been recommended. Intestinal ALP isoenzyme, an asialoglycoprotein normally cleared by the hepatic asialoglycoprotein receptors, is often increased in patients with liver cirrhosis.

**Reference Values:**

**Males**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>ALP Range (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14 days</td>
<td>83-248 U/L</td>
</tr>
<tr>
<td>15 days- &lt;1 year</td>
<td>122-469 U/L</td>
</tr>
<tr>
<td>1-&lt;10 years</td>
<td>142-335 U/L</td>
</tr>
<tr>
<td>10-&lt;13 years</td>
<td>129-417 U/L</td>
</tr>
<tr>
<td>13-&lt;15 years</td>
<td>116-468 U/L</td>
</tr>
<tr>
<td>15-&lt;17 years</td>
<td>82-331 U/L</td>
</tr>
<tr>
<td>17-&lt;19 years</td>
<td>55-149 U/L</td>
</tr>
<tr>
<td>&gt; or =19 years</td>
<td>40-129 U/L</td>
</tr>
</tbody>
</table>

**Females**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>ALP Range (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14 days</td>
<td>83-248 U/L</td>
</tr>
<tr>
<td>15 days- &lt;1 year</td>
<td>122-469 U/L</td>
</tr>
<tr>
<td>1-&lt;10 years</td>
<td>142-335 U/L</td>
</tr>
<tr>
<td>10-&lt;13 years</td>
<td>129-417 U/L</td>
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<tr>
<td>13-&lt;15 years</td>
<td>57-254 U/L</td>
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<tr>
<td>15-&lt;17 years</td>
<td>50-117 U/L</td>
</tr>
<tr>
<td>&gt; or =17 years</td>
<td>35-104 U/L</td>
</tr>
</tbody>
</table>

**Clinical References:**

Alkaline Phosphatase, Total and Isoenzymes, Serum

Clinical Information: Alkaline phosphatase (ALP) is present in a number of tissues including liver, bone, intestine, and placenta. The activity of ALP found in serum is a composite of isoenzymes from those sites and, in some circumstances, placental or Regan isoenzymes. Serum ALP is of interest in the diagnosis of 2 main groups of conditions-hepatobiliary disease and bone disease associated with increased osteoblastic activity. A rise in ALP activity occurs with all forms of cholestasis, particularly with obstructive jaundice. The response of the liver to any form of biliary tree obstruction is to synthesize more ALP. The main site of new enzyme synthesis is the hepatocytes adjacent to the biliary canaliculi. ALP also is elevated in disorders of the skeletal system that involve osteoblast hyperactivity and bone remodeling, such as Paget's disease, rickets and osteomalacia, fractures, and malignant tumors. Moderate elevation of ALP may be seen in other disorders such as Hodgkin's disease, congestive heart failure, ulcerative colitis, regional enteritis, and intra-abdominal bacterial infections.

Useful For: Diagnosis and treatment of liver, bone, intestinal, and parathyroid diseases Determining the tissue source of increased alkaline phosphatase (ALP) activity in serum Differentiating between liver and bone sources of elevated ALP

Interpretation: Total Alkaline Phosphatase (ALP): ALP elevations tend to be more marked (more than 3-fold) in extrahepatic biliary obstructions (eg, by stone or cancer of the head of the pancreas) than in intrahepatic obstructions, and the more complete the obstruction, the greater the elevation. With obstruction, serum ALP activities may reach 10 to 12 times the upper limit of normal, returning to normal upon surgical removal of the obstruction. The ALP response to cholestatic liver disease is similar to the response of gamma-glutamyltransferase (GGT), but more blunted. If both GGT and ALP are elevated, a liver source of the ALP is likely. Among bone diseases, the highest level of ALP activity is encountered in Paget's disease, as a result of the action of the osteoblastic cells as they try to rebuild bone that is being resorbed by the uncontrolled activity of osteoclasts. Values from 10 to 25 times the upper limit of normal are not unusual. Only moderate rises are observed in osteomalacia, while levels are generally normal in osteoporosis. In rickets, levels 2 to 4 times normal may be observed. Primary and secondary hyperparathyroidism are associated with slight to moderate elevations of ALP; the existence and degree of elevation reflects the presence and extent of skeletal involvement. Very high enzyme levels are present in patients with osteogenic bone cancer. A considerable rise in ALP is seen in children following accelerated bone growth. ALP increases of 2 to 3 times normal may be observed in women in the third trimester of pregnancy, although the reference interval is very wide and levels may not exceed the upper limit of normal in some cases. In pregnancy, the additional enzyme is of placental origin. ALP Isoenzymes: Liver ALP isoenzyme is associated with biliary epithelium and is elevated in cholestatic processes. Various liver diseases (primary or secondary cancer, biliary obstruction) increase the liver isoenzyme. Liver 1 (L1) is increased in some nonmalignant diseases (such as cholestasis, cirrhosis, viral hepatitis and in various biliary and hepatic pathologies). It is also increased in malignancies with hepatic metastasis, in cancer of the lungs and digestive tract and in lymphoma. An increase of liver 2 (L2) may occur in cholestasis and biliary diseases (eg, cirrhosis, viral hepatitis) and in malignancies (eg, breast, liver, lung, prostate, digestive tract) with liver metastasis. Osteoblastic bone tumors and hyperactivity of osteoblasts involved in bone remodeling (eg, Paget disease) increase the bone isoenzyme. Paget disease leads to a striking, solitary elevation of bone ALP. The intestinal isoenzyme may be increased in patients with cirrhosis and in individuals who are blood group O or B secretors. The placental (carcinoplacental antigen) and Regan isoenzyme can be elevated in cancer patients.

Reference Values:

ALKALINE PHOSPHATASE
Males
0-14 days: 83-248 U/L
15 days-<1 year: 122-469 U/L
1-<10 years: 142-335 U/L
10-<13 years: 129-417 U/L
13-<15 years: 116-468 U/L
15-<17 years: 82-331 U/L

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
17-<19 years: 55-149 U/L
> or =19 years: 40-129 U/L

Females
0-14 days: 83-248 U/L
15 days-<1 year: 122-469 U/L
1-<10 years: 142-335 U/L
10-<13 years: 129-417 U/L
13-<15 years: 57-254 U/L
15-<17 years: 50-117 U/L
> or =17 years: 35-104 U/L

ALKALINE PHOSPHATASE ISOENZYMES
Liver 1%
0-6 years: 5.1-49.0%
7-9 years: 3.0-45.0%
10-13 years: 2.9-46.3%
14-15 years: 7.8-48.9%
16-18 years: 14.9-50.5%
> or =19 years: 27.8-76.3%
Liver 1
0-6 years: 7.0-112.7 IU/L
7-9 years: 7.4-109.1 IU/L
10-13 years: 7.8-87.6 IU/L
14-15 years: 10.3-75.6 IU/L
16-18 years: 13.7-78.5 IU/L
> or =19 years: 16.2-70.2 IU/L
Liver 2%
0-6 years: 2.9-13.7%
7-9 years: 3.7-12.5%
10-13 years: 2.9-22.3%
14-15 years: 2.2-19.8%
16-18 years: 1.9-12.5%
> or =19 years: 0.0-8.0%
Liver 2
0-6 years: 3.0-41.5 IU/L
7-9 years: 4.0-35.6 IU/L
10-13 years: 3.3-37.8 IU/L
14-15 years: 2.2-32.1 IU/L
16-18 years: 1.4-19.7 IU/L
> or =19 years: 0.0-5.8 IU/L
Bone %
0-6 years: 41.5-82.7%
7-9 years: 39.9-85.8%
10-13 years: 31.8-91.1%
14-15 years: 30.6-85.4%
16-18 years: 38.9-72.6%
> or =19 years: 19.1-67.7%
Bone
0-6 years: 43.5-208.1 IU/L
7-9 years: 41.0-258.3 IU/L
10-13 years: 39.4-346.1 IU/L
14-15 years: 36.4-320.5 IU/L
16-18 years: 32.7-214.6 IU/L
> or =19 years: 12.1-42.7 IU/L
Intestine %
0-6 years: 0.0-18.4%
7-9 years: 0.0-18.3%
10-13 years: 0.0-11.8%
14-15 years: 0.0-8.2%
16-18 years: 0.0-8.7%
> or =19 years: 0.0-20.6%

Intestine
0-6 years: 0.0-37.7 IU/L
7-9 years: 0.0-45.6 IU/L
10-13 years: 0.0-40.0 IU/L
14-15 years: 0.0-26.4 IU/L
16-18 years: 0.0-12.7 IU/L
> or =19 years: 0.0-11.0 IU/L

Placental
Not present


FABP2

Allergic Bronchopulmonary Aspergillosis Panel II

Interpretation: Total IgE Age Related Reference Range 1-11 months 0-12 1 year 0-15 2 year 1-29 3 year 4-35 4 year 2-33 5 year 8-56 6 year 3-95 7 year 2-88 8 year 5-71 9 year 3-88 10 year 7-110 11-14 year 7-111 15-19 year 6-96 20-30 year 4-59 31-50 year 5-79 51-80 year 3-95 8 year 2-88 9 year 5-71 10 year 3-88 10 year 7-110 11-14 year 7-111 15-19 year 6-96 20-30 year 4-59 31-50 year 5-79 51-80 year 3-48 Aspergillus fumigatus IgE Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal 1 0.35-0.69 Low Positive 2 0.70-3.4 Moderate Positive 3 3.5-17.4 High Positive 4 17.5-49.9 Very High Positive 5 50.0-99.9 Very High Positive 6 > 100 Very High Positive Aspergillus fumigatus IgG mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:

Immunoglobulin E (IgE)
Age Related Reference Range
1-11 months 0-12
1 year 0-15
2 year 1-29
3 year 4-35
4 year 2-33
5 year 8-56
6 year 3-95
7 year 2-88
8 year 5-71
9 year 3-88
10 year 7-110
11-14 year 7-111
15-19 year 6-96
20-30 year 4-59
31-50 year 5-79
51-80 year 3-48

Aspergillus fumigatus IgE <0.35 kU/L

Aspergillus fumigatus IgG <46 mcg/mL

A. fumigatus Mix Gel Diffusion Negative

The gel diffusion method was used to test this patient’s serum for the presence of precipitating antibodies (IgG) to the antigens indicated. These antibodies are serological markers for exposure and
immunological sensitization. The clinical significance varies, depending on the history and symptoms. This test was developed and its performance characteristics determined by Viracor Eurofins. It has not been cleared or approved by the FDA.

Patients with allergic bronchopulmonary aspergillosis (ABPA) are expected to have the following serological features:

1) A high total IgE of >500 IU/mL, unless patient is receiving corticosteroids.
2) An elevated Aspergillus-specific IgE of class 4 or higher.
3) Positive for Aspergillus-specific IgG.

**Allo-isoleucine, Blood Spot**

**Clinical Information:** Maple-syrup urine disease (MSUD) is an inborn error of metabolism caused by the deficiency of the branched-chain-ketoacid dehydrogenase (BCKDH) complex. The BCKDH complex is involved in the metabolism of the branched-chain amino acids (BCAA); isoleucine (Ile), leucine (Leu), and valine (Val). Classic MSUD presents in the neonate with feeding intolerance, failure to thrive, vomiting, lethargy, and maple-syrup odor to urine and cerumen. If untreated, it progresses to irreversible mental retardation, hyperactivity, failure to thrive, seizures, coma, cerebral edema, and possibly death. MSUD is a pan-ethnic condition, but is most prevalent in the Old Order Mennonite community in Lancaster, Pennsylvania with an incidence there of 1:760 live births. The incidence of MSUD is approximately 1:200,000 live births in the general population. Newborn screening includes the measurement of BCAA (Leu, Ile, and Val), which are elevated in MSUD. However, unaffected infants receiving total parenteral nutrition frequently have increased levels of BCAA, a situation that often triggers unnecessary follow-up investigations. Abnormal concentrations of allo-isoleucine (Allo-Ile) are pathognomonic for MSUD. The determination of Allo-Ile (second-tier testing) in the same newborn screening specimens that reveals elevated BCAA allows for positive identification of patients with MSUD and differentiation from BCAA elevations due to dietary artifacts, reducing the occurrence of false-positive newborn screening results. Treatment of MSUD aims to normalize the concentration of BCAA by dietary restriction of these amino acids. Because BCAA belong to the essential amino acids, the dietary treatment requires frequent adjustment, which is accomplished by regular determination of BCAA and Allo-Ile concentrations.

**Useful For:** Evaluation of newborn screening specimens that test positive for branched-chain amino acids elevations Follow-up of patients with maple-syrup urine disease

**Interpretation:** Allo-isoleucine is nearly undetectable in individuals not affected by maple-syrup urine disease (MSUD). Accordingly, its presence is diagnostic for MSUD, and its absence is sufficient to rule-out MSUD.

**Reference Values:**
Allo-isoleucine: <2 nmol/mL
Leucine: 35-215 nmol/mL
Isoleucine: 13-130 nmol/mL
Valine: 51-325 nmol/mL

An interpretive report will also be provided.

**Clinical References:**
Almond Food IgG

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation* 2.0 Upper Limit of Quantitation** 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Almond, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>
ALPS 82449

**Alpha Beta Double-Negative T Cells for Autoimmune Lymphoproliferative Syndrome**

**Clinical Information:** Autoimmune lymphoproliferative syndrome (ALPS) (also known as Canale-Smith syndrome) is a complex clinical disorder of dysregulated lymphocyte homeostasis that is characterized by lymphoproliferative disease, autoimmune cytopenias, splenomegaly, and lymphadenopathy with an increased susceptibility to malignancy. Typically, ALPS is diagnosed by childhood or young adulthood. Genetic defects in the apoptosis (programmed cell death) pathway have been determined for most cases of ALPS. Apoptosis plays a role in normal immune homeostasis by limiting lymphocyte accumulation and autoimmune reactivity. The interaction of the surface receptor CD95 (FAS) and its ligand (CD95L; FASL) triggers the apoptotic pathway in lymphocytes. The following molecular ALPS classification has been established: ALPS Classification Molecular/Genetic Defect in Apoptosis Type Ia CD95 (FAS) mutations(1) Type Ib Heterozygous CD95L (FASLG) mutations(1) Type Ic Homozygous CD95L (FASLG) mutation(2) Type II CASP8 or CASP10 mutations(1,3) Type III Unknown(1,3) Patients with ALPS have an increase in a normally rare population of T cells (typically <1%) that are alpha beta T-cell receptor (TCR)-positive, as well as negative for both CD4 and CD8 coreceptors (double-negative T cells: DNT).(1) The alpha beta TCR+DNT cells from ALPS patients also express an unusual B-cell-specific CD45R isoform, called B220.(4,5) B220 expression on alpha beta TCR+DNT cells has been demonstrated to be a sensitive and specific marker for ALPS and is associated with FAS mutations.(4) Several other diseases can present with an ALPS-like phenotype, including independent conditions like Evans syndrome (a combination of autoimmune hemolytic anemia and autoimmune thrombocytopenic purpura), Rosai-Dorfman disease (massive painless cervical lymphadenopathy that may be accompanied by leukocytosis, elevated erythrocyte sedimentation rate, and hypergammaglobulinemia), and nodular lymphocyte-predominant Hodgkin disease.(1)

**Useful For:** Diagnosing autoimmune lymphoproliferative syndrome, primarily in patients <45 years of age

**Interpretation:** The presence of increased circulating T cells (CD3+) that are negative for CD4 and CD8 (double-negative T cells: DNT) and positive for the alpha/beta T-cell receptor (TCR) is required for the diagnosis of autoimmune lymphoproliferative syndrome (ALPS). The laboratory finding of increased alpha beta TCR+DNT cells is consistent with ALPS only with the appropriate clinical picture (nonmalignant lymphadenopathy, splenomegaly, and autoimmune cytopenias). Conversely, there are other immunological disorders, including common variable immunodeficiency (CVID), which have subsets for patients with this clinical picture, but no increase in alpha beta TCR+DNT cells. If the percent of the absolute count of either the alpha beta TCR+DNT cells or alpha beta TCR+DNT B220+ cells is abnormal, additional testing is indicated. All abnormal alpha beta TCR+DNT cell results should be confirmed (for ALPS) with additional testing for defective in vitro lymphocyte apoptosis, followed by confirmatory genetic testing for FAS mutations (call 800-533-1710 for test forwarding information).

**Reference Values:**

**Alpha beta TCR+DNT cells**

- 2-18 years: <2% CD3 T cells
- 19-70+ years: <3% CD3 T cells

Reference values have not been established for patients that are less than 24 months of age.

**Alpha beta TCR+DNT B220+ cells**

- 2-18 years: <0.4% CD3 T cells
19-70+ years: <0.3% CD3 T cells
Reference values have not been established for patients that are less than 24 months of age.

Alpha beta TCR+DNT B220+ cells
2-18 years: <7 cells/mcL
19-70+ years: <6 cells/mcL
Reference values have not been established for patients that are less than 24 months of age.


AFSH 71768

Alpha FSH Immunostain, Technical Component Only

Clinical Information: Follicle stimulating hormone (FSH) alpha subunit is a component common to all of the glycoprotein hormones produced by the anterior pituitary (luteinizing hormone [LH], thyroid-stimulating hormone [TSH], and FSH). Glycoprotein hormone-producing cells (approximately 30% of the total cell population) in normal pituitary stain in a cytoplasmic pattern. Immunohistochemical detection of alpha-FSH may be useful in the classification of pituitary adenomas.

Useful For: The study of pituitary adenomas

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


WASQR 47958

Alpha Globin Gene Sequencing, Blood

Clinical Information: Alpha-globin gene sequencing detects alpha-globin variants and nondeletional alpha-thalassemia mutations. Alpha-thalassemia is the most common monogenic condition in the world. It is estimated that up to 5% of the world's population carries at least 1 alpha-thalassemia mutation and, in the United States, approximately 30% of African Americans are thought to carry an alpha-thalassemia mutation. Alpha-thalassemia mutations are most common in...
Alpha Globin Gene Sequencing, Blood

**Clinical Information:** Alpha globin gene sequencing detects alpha globin variants and nondeletional alpha thalassemia mutations. Alpha thalassemia is the most common monogenic condition in the world. It is estimated that up to 5% of the world’s population carries at least 1 alpha thalassemia mutation and, in the United States, approximately 30% of African Americans are thought to carry an alpha thalassemia mutation. Alpha thalassemia mutations are most common in individuals of Southeast Asian, African, Mediterranean, Indian, and Middle-Eastern descent, but they can be found in persons from any ethnic group. Four alpha-globin genes are normally present, 2 copies on each chromosome 16. Alpha-thalassemia mutations result in decreased alpha-globin chain production. In general, alpha-thalassemia is characterized by hypochromic, microcytic anemia and varies clinically from asymptomatic (alpha-thalassemia silent carrier and alpha-thalassemia trait) to lethal hemolytic anemia (hemoglobin [Hb] Barts hydrops fetalis). Large deletions of the alpha-globin genes account for approximately 90% of alpha-thalassemia mutations, and these mutations will not be detected by alpha-globin gene sequencing. Other mutations, such as point mutations or small deletions within the alpha-globin genes, account for most of the remaining 10% of alpha-thalassemia mutations. These nondeletional subtypes can be detected by alpha-globin gene sequencing. The most common nondeletional alpha-thalassemia mutation is Hb Constant Spring (Hb CS). The majority of alpha-globin chain variants are clinically and hematologically benign; however, some cause erythrocytosis and chronic hemolytic anemia. Hemoglobin electrophoresis may not be able to confirm their identity. In these instances alpha-globin gene sequencing can be useful.


**Interpretation:** An summary interpretation will be provided as a part of the HAEVP / Hemolytic Anemia Evaluation; HBEHC / Hemoglobin Electrophoresis Cascade, Blood; MEVP / Methemoglobinemia Evaluation; REVE / Erythrocytosis Evaluation; THEVP / Thalassemia and Hemoglobinopathy Evaluation.

**Reference Values:**
Only orderable as a reflex. For more information see:
-HAEVP / Hemolytic Anemia Evaluation
-HBEHC / Hemoglobin Electrophoresis Cascade, Blood
-MEVP / Methemoglobinemia Evaluation
-REVE / Erythrocytosis Evaluation
-THEVP / Thalassemia and Hemoglobinopathy Evaluation

**Clinical References:**
confirm their identity. In these instances alpha globin gene sequencing can be useful.

**Useful For:** Diagnosing nondeletional alpha thalassemia Testing for nondeletional alpha thalassemia in a symptomatic individual Follow-up testing to an abnormal hemoglobin electrophoresis that identified an alpha globin chain variant

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**FALG** 57663

**Alpha Lactalbumin IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
< 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**ASYN** 70635

**Alpha Synuclein Immunostain, Technical Component Only**

**Clinical Information:** Alpha synuclein is a member of a family of cytoplasmic proteins found predominantly in the presynaptic nerve terminal of the brain. Synucleins are thought to be involved in neuronal plasticity, synaptic function, and neurodegenerative disease. Alpha-synuclein is abundant in Lewy bodies in sporadic Parkinson disease and dementia with Lewy bodies. It is a major component of amyloid plaques in Alzheimer disease.

**Useful For:** Identification of alpha synuclein in neurogenerative disorders

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
**FA1GP**  
**Alpha-1-Acid Glycoprotein**  
**Reference Values:**  
Adults: 39–115 mg/dL

**AATRP**  
**Alpha-1-Antitrypsin (AAT) Immunostain, Technical Component Only**  
**Clinical Information:** Alpha-1-antitrypsin (AAT) is a plasma protein synthesized in the liver and is present in serum and tissue fluids where it acts as an inhibitor of proteases, especially elastase. AAT deficiency is associated with development of emphysema and liver disease. In liver disease, abnormal accumulation of AAT is seen as cytoplasmic globules in hepatocytes.  
**Useful For:** Identification of abnormal accumulation of alpha-1-antitrypsin  
**Interpretation:** The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.  

**CA1A**  
**Alpha-1-Antitrypsin Clearance, Feces and Serum**  
**Clinical Information:** Alpha-1-antitrypsin (A1A) is resistant to degradation by digestive enzymes and is, therefore, used as an endogenous marker for the presence of blood proteins in the intestinal tract. A1A clearance is reliable for measuring protein loss distal to the pylorus. Gastrointestinal protein enteropathy has been associated with regional enteritis, sprue, Whipple intestinal lipodystrophy, gastric carcinoma, allergic gastroenteropathy, intestinal lymphangiectasia, constrictive pericarditis, congenital hypogammaglobulinemia, and iron deficiency anemia associated with intolerance to cow's milk.  
**Useful For:** Diagnosing protein-losing enteropathies  
**Interpretation:** Elevated alpha-1-antitrypsin (A1A) clearance suggests excessive gastrointestinal protein loss. (The positive predictive value of the test has been found to be 97.7% and the negative predictive value is 75%.) Patients with protein-losing enteropathies generally have A1A clearance values greater than 50 mL/24 hours and A1A stool concentrations above 100 mg/mL. Borderline elevations above the normal range are equivocal for protein-losing enteropathies.  
**Reference Values:**  
Clearance: < or =27 mL/24 hours  
Fecal alpha-1-antitrypsin concentration: < or =54 mg/dL  
Serum alpha-1-antitrypsin concentration: 100-190 mg/dL  
Alpha-1-Antitrypsin Phenotype

**Clinical Information:** Alpha-1-antitrypsin (A1A) is the most abundant serum protease inhibitor and inhibits trypsin and elastin, as well as several other proteases. The release of proteolytic enzymes from plasma onto organ surfaces and into tissue spaces results in tissue damage unless inhibitors are present. Congenital deficiency of A1A is associated with the development of emphysema at an unusually early age and with an increased incidence of neonatal hepatitis, usually progressing to cirrhosis. Most normal individuals have the M phenotype (M, M1, or M2). Over 99% of M phenotypes are genetically MM. In the absence of family studies, the phenotype (M) and quantitative level can be used to infer the genotype (MM). The most common alleles associated with a quantitative deficiency are Z and S. See Alpha-1-Antitrypsin-A Comprehensive Testing Algorithm in Special Instructions.

**Useful For:** Identification of homozygous and heterozygous phenotypes of the alpha-1-antitrypsin deficiency

**Interpretation:** There are >40 alpha-1-antitrypsin (A1A) phenotypes (most of these are associated with normal quantitative levels of protein). The most common normal phenotype is M (M, M1, or M2), and >90% of Caucasians are genetically homozygous M (MM). A1A deficiency is usually associated with the Z phenotype (homozygous ZZ), but SS and SZ are also associated with decreased A1A levels.

**Reference Values:**
- ALPHA-1-ANTITRYPSIN
  - 100-190 mg/dL

  **ALPHA-1-ANTITRYPSIN PHENOTYPE**
  - The interpretive report will identify the alleles present. For rare alleles, the report will indicate whether or not they have been associated with reduced quantitative levels of alpha-1-antitrypsin.

**Clinical References:**

Alpha-1-Antitrypsin Proteotype S/Z by LC-MS/MS, Serum

**Clinical Information:** Alpha-1-antitrypsin (A1A) is a protein that inhibits the enzyme neutrophil elastase. It is predominantly synthesized in the liver and secreted into the bloodstream. The inhibition function is especially important in the lungs because it protects against excess tissue degradation. Tissue degradation due to A1A deficiency is associated with an increased risk for early onset panlobular emphysema, which initially affects the lung bases (as opposed to smoking-related emphysema, which presents with upper-lung field emphysema). Patients may become symptomatic in their 30s and 40s. The most frequent symptoms reported in a National Institute of Health study of 1,129 patients with severe deficiency (mean age 46 years) included cough (42%), wheezing (65%), and dyspnea with exertion (84%). Many patients were misdiagnosed as having asthma. It is estimated that approximately one-sixth of all lung transplants are for A1A deficiency. Liver disease can also occur, particularly in children; it occurs much less commonly than emphysema in adults. A1A deficiency is a relatively common disorder in Northern European Caucasians. The diagnosis of A1A deficiency is initially made by quantitation of protein levels in serum followed by determination of specific allelic variants by isoelectric focusing (IEF). While there are many different alleles in this gene, only 3 are common. The 3 major alleles include: M (full functioning, normal allele), S (associated with reduced levels of protein), and Z (disease-causing mutation associated with liver disease and premature emphysema). The S and Z alleles account for the majority of the abnormal alleles detected in affected patients. As a codominant disorder, both alleles are expressed. An individual of SZ or S-null genotype may have a small increased...
risk for emphysema (but not liver disease) due to slightly reduced protein levels. On the other hand, an individual with the ZZ genotype is at greater risk for early onset liver disease and premature emphysema. Smoking appears to hasten development of emphysema by 10 to 15 years. These individuals should be monitored closely for lung and liver function. Historically, IEF has been the primary method for characterizing variants, though in some cases the interpretation is difficult and prone to error. Serum quantitation is helpful in establishing a diagnosis, but can be influenced by other factors. A proteomic method using trypsin-digested sera can detect the mutated peptides of the S and Z alleles, but can miss disease alleles other than the S and Z alleles. This test combines all of these methods to provide a comprehensive result.

Useful For: Determining the specific proteotype for prognosis and genetic counseling for patients with alpha-1-antitrypsin deficiency

Interpretation: For each of the possible alpha-1-antitrypsin (A1A) genotypes there is an expected range for the total serum level of A1A. However, a number of factors can influence either the A1A serum level or the A1A proteotype results, including acute illness (A1A is an acute-phase reactant), protein replacement therapy, the presence of other rare variants, or the presence of DNA polymorphisms. When the serum level differs from what is expected for that proteotype (ie, discordant), additional studies are performed to ensure the most appropriate interpretation of test results. Additional follow-up may include A1A phenotyping by isoelectric focusing, obtaining additional clinical information, and DNA sequencing. See Alpha-1-Antitrypsin Reflex Table in Special Instructions.

Reference Values:

ALPHA-1-ANTITRYPSIN
100-190 mg/dL

ALPHA-1-ANTITRYPSIN PROTEOTYPE
Negative for S and Z phenotype (Non S Non Z)


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**A1AF**

**Alpha-1-Antitrypsin, Random, Feces**

Clinical Information: Alpha-1-antitrypsin (A1A) is resistant to degradation by digestive enzymes and is, therefore, used as an endogenous marker for the presence of blood proteins in the intestinal tract. A1A clearance is reliable for measuring protein loss distal to the pylorus. Gastrointestinal protein enteropathy has been associated with regional enteritis, sprue, Whipple intestinal lipodystrophy, gastric carcinoma, allergic gastroenteropathy, intestinal lymphangiectasia, constrictive pericarditis, congenital hypogammaglobulinemia, and iron deficiency anemia associated with intolerance to cow's milk.

Useful For: Diagnosing protein-losing enteropathies, especially when used in conjunction with serum alpha-1-antitrypsin (A1A) levels as a part of A1A clearance studies

Interpretation: Patients with protein-losing enteropathies generally have alpha-1-antitrypsin stool concentrations over 100 mg/mL. Borderline elevations above the normal range are equivocal for protein-losing enteropathies.

Reference Values:
< or =54 mg/dL

**Alpha-1-Antitrypsin, Serum**

**Clinical Information:** Alpha-1-antitrypsin (A1A) is the most abundant serum protease inhibitor and inhibits trypsin and elastin, as well as several other proteases. The release of proteolytic enzymes from plasma onto organ surfaces and into tissue spaces results in tissue damage unless inhibitors are present. Congenital deficiency of A1A is associated with the development of emphysema at an unusually early age and with an increased incidence of neonatal hepatitis, usually progressing to cirrhosis. See Alpha-1-Antitrypsin-A Comprehensive Testing Algorithm in Special Instructions.

**Useful For:** Workup of individuals with suspected disorders such as familial chronic obstructive lung disease Diagnosis of alpha-1-antitrypsin deficiency

**Interpretation:** Patients with serum levels <70 mg/dL may have a homozygous deficiency and are at risk for early lung disease. Alpha-1-antitrypsin proteotyping should be done to confirm the presence of homozygous deficiency alleles. If clinically indicated, patients with serum levels <125 mg/dL should be proteotyped in order to identify heterozygous individuals. Heterozygotes do not appear to be at increased risk for early emphysema.

**Reference Values:**
100-190 mg/dL


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**Alpha-1-Microglobulin, 24 Hour, Urine**

**Clinical Information:** Alpha-1-microglobulin is a low-molecular-weight protein of 26 kDa and a member of the lipocalin protein superfamily. (1) It is synthesized in the liver, freely filtered by glomeruli, and reabsorbed by renal proximal tubules cells where it is catabolized. (1) Due to extensive tubular reabsorption, under normal conditions very little filtered alpha-1-microglobulin appears in the final excreted urine. Therefore, an increase in the urinary concentration of alpha-1-microglobulin indicates proximal tubule injury and/or impaired proximal tubular function. Elevated excretion rates can indicate tubular damage associated with renal tubulointerstitial nephritis or tubular toxicity from heavy metal or nephrotoxic drug exposure. Glomerulonephropathies and renal vasculopathies also are often associated with coexisting tubular injury and so may result in elevated excretion. Elevated alpha-1-microglobulin in patients with urinary tract infections may indicate renal involvement (pyelonephritis). Measurement of urinary excretion of retinol-binding protein, another low-molecular-weight protein, is an alternative to the measurement of alpha-1-microglobulin. To date, there are no convincing studies to indicate that one test has better clinical utility than the other. Urinary excretion of alpha-1-microglobulin can be determined from either a 24-hour collection or from a random urine collection. The 24-hour collection is traditionally considered the gold standard. For random or spot collections, the concentration of alpha-1-microglobulin is divided by the urinary creatinine concentration. This corrected value adjusts alpha-1-microglobulin for variabilities in urine concentration.

**Useful For:** Assessment of renal tubular injury or dysfunction Screening for tubular abnormalities Detecting chronic asymptomatic renal tubular dysfunction

**Interpretation:** Alpha-1-microglobulin above the reference values may be indicative of a proximal tubular dysfunction.

**Reference Values:**
> or =16 years: <19 mg/24 hours
7 mg/g creatinine is a literature suggested upper reference limit for pediatrics 1 month to 15 years of age.
Alpha-1-Microglobulin, Random, Urine

Clinical Information: Alpha-1-microglobulin is a low-molecular-weight protein of 26 kDa and a member of the lipocalin protein superfamily. It is synthesized in the liver, freely filtered by glomeruli, and reabsorbed by renal proximal tubules where it is catabolized. Due to extensive tubular reabsorption, under normal conditions very little filtered alpha-1-microglobulin appears in the final excreted urine. Therefore, an increase in the urinary concentration of alpha-1-microglobulin indicates proximal tubule injury and/or impaired proximal tubular function. Elevated excretion rates can indicate tubular damage associated with renal tubulointerstitial nephritis or tubular toxicity from heavy metal or nephrotoxic drug exposure. Glomerulonephropathies and renal vasculopathies also are often associated with coexisting tubular injury and so may result in elevated urinary alpha-1-microglobulin excretion. Elevated alpha-1-microglobulin in patients with urinary tract infections may indicate renal involvement (pyelonephritis). Measurement of urinary excretion of retinol-binding protein, another low-molecular-weight protein, is an alternative to the measurement of alpha-1-microglobulin. To date, there are no convincing studies to indicate that 1 test has better clinical utility than the other. Urinary excretion of alpha-1-microglobulin can be determined from either a 24-hour collection or from a random urine collection. The 24-hour collection is traditionally considered the gold standard. For random or spot collections, the concentration of alpha-1-microglobulin is divided by the urinary creatinine concentration. This corrected value adjusts alpha-1-microglobulin for variabilities in urine concentration.

Useful For: Assessment of renal tubular injury or dysfunction Screening for tubular abnormalities Detecting chronic asymptomatic renal tubular dysfunction

Interpretation: Alpha-1-microglobulin above the reference values may indicate a proximal tubular dysfunction. As suggested in the literature, 7 mg/g creatinine is an upper reference limit for pediatric patients of 1 month to 15 years of age.

Reference Values:
<50 years: <13 mg/g creatinine
> or = 50 years: <20 mg/g creatinine

Useful For: Diagnosing congenital alpha-2 plasmin inhibitor deficiencies (rare) Providing a more complete assessment of disseminated intravascular coagulation, intravascular coagulation and fibrinolysis, or hyperfibrinolysis (primary fibrinolysis), when measured in conjunction with fibrinogen, fibrin D-dimer, fibrin degradation products, soluble fibrin monomer complex, and plasminogen Evaluating liver disease Evaluating the effects of fibrinolytic or antifibrinolytic therapy

Interpretation: Patients with congenital homozygous deficiency (with levels of <10%) are clinically affected (bleeding). Heterozygotes having levels of 30% to 60% of mean normal activity are usually asymptomatic. Lower than normal levels may be suggestive of consumption due to activation of plasminogen and its inhibition by alpha-2 plasmin inhibitor. The clinical significance of high levels of alpha-2 plasmin inhibitor is unknown.

Reference Values:
Adults: 80-140%

Normal, full-term newborn infants may have borderline low or mildly decreased levels (> or =50%) which reach adult levels within 5 to 7 days postnatal.*
Healthy, premature infants (30-36 weeks gestation) may have mildly decreased levels which reach adult levels in < or =90 days postnatal.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.


Alpha-2-Macroglobulin, Serum

Clinical Information: Alpha-2-macroglobulin is a protease inhibitor and is 1 of the largest plasma proteins. It transports hormones and enzymes, exhibits effector and inhibitor functions in the development of the lymphatic system, and inhibits components of the complement system and hemostasis system. Increased levels of alpha-2-macroglobulin are found in nephrotic syndrome when other lower molecular weight proteins are lost and alpha-2-macroglobulin is retained because of its large size. In patients with liver cirrhosis and diabetes, the levels are found to be elevated. Patients with acute pancreatitis exhibit low serum concentrations which correlate with the severity of the disease. In hyperfibrinolytic states, after major surgery, in septicemia and severe hepatic insufficiency, the measured levels of alpha-2-macroglobulin are often low. Acute myocardial infarction patients with low alpha-2-macroglobulin have been reported to have a significantly better prognosis with regard to the >1 year survival time.

Useful For: Evaluation of patients with nephrotic syndrome and pancreatitis

Interpretation: Values are elevated in the nephrotic syndrome in proportion to the severity of protein loss (lower molecular weight). Values are low in proteolytic diseases such as pancreatitis.

Reference Values:
100-280 mg/dL

Alpha-Amylase, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>


Alpha-Fetoprotein (AFP) Immunostain, Technical Component Only

Clinical Information: Alpha-fetoprotein (AFP) is an oncofetal antigen normally expressed in fetal liver, but not present in normal adult tissues. AFP can be expressed in yolk sac tumors and in hepatocellular carcinomas.

Useful For: Aids in the identification of yolk sac tumors and hepatocellular carcinoma

Interpretation: The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified...
**Clinical References:**
Alpha-Fetoprotein (AFP) Tumor Marker, Serum

Clinical Information: Alpha-fetoprotein (AFP) is a glycoprotein that is produced in early fetal life by the liver and by a variety of tumors including hepatocellular carcinoma, hepatoblastoma, and nonseminomatous germ cell tumors of the ovary and testis (eg, yolk sac and embryonal carcinoma). Most studies report elevated AFP concentrations in approximately 70% of patients with hepatocellular carcinoma. Elevated AFP concentrations are found in 50% to 70% of patients with nonseminomatous testicular tumors. (1) AFP is elevated during pregnancy. Persistence of AFP in the mother following birth is a rare hereditary condition. (2) Neonates have markedly elevated AFP levels (>100,000 ng/mL) that rapidly fall to below 100 ng/mL by 150 days and gradually return to normal over their first year. (2) Concentrations of AFP above the reference range also have been found in serum of patients with benign liver disease (eg, viral hepatitis, cirrhosis), gastrointestinal tract tumors and, along with carcinoembryonic antigen in ataxia telangiectasia. The biological half-life of AFP is approximately 5 days.

Useful For: The follow-up management of patients undergoing cancer therapy, especially for testicular and ovarian tumors and for hepatocellular carcinoma. Often used in conjunction with human chorionic gonadotropin (2)

Interpretation: Alpha-fetoprotein (AFP) levels may be elevated in association with a variety of malignancies or benign diseases. Failure of the AFP value to return to normal by approximately 1 month after surgery suggests the presence of residual tumor. Elevation of AFP after remission suggests tumor recurrence; however, tumors originally producing AFP may recur without an increase in AFP.

Reference Values:
<6.0 ng/mL
Reference values are for nonpregnant subjects only; fetal production of AFP elevates values in pregnant women.

Range for newborns is not available, but concentrations over 100,000 ng/mL have been reported in normal newborns, and the values rapidly decline in the first 6 months of life. (See literature reference: Ped Res 1981;15:50-52) For further interpretive information, see Alpha-Fetoprotein (AFP) in Special Instructions.

Serum markers are not specific for malignancy, and values may vary by method.


Alpha-Fetoprotein (AFP), Peritoneal Fluid

Clinical Information: Malignancy accounts for approximately 7% of cases of ascites formation. Malignant disease can cause ascites by various mechanisms including: peritoneal carcinomatosis (53%), massive liver metastasis causing portal hypertension (13%), peritoneal carcinomatosis plus massive liver metastasis (13%), hepatocellular carcinoma plus cirrhosis (7%), and chylous ascites due to lymphoma (7%). The evaluation and diagnosis of malignancy-related ascites is based on the patient clinical history,
ascites fluid analysis, and imaging tests. The overall sensitivity of cytology for the detection of malignancy-related ascites ranges from 58% to 75%. Cytology examination is most successful in patients with ascites related to peritoneal carcinomatosis as viable malignant cells are exfoliated into the ascitic fluid. However, only approximately 53% of patients with malignancy-related ascites have peritoneal carcinomatosis. Patients with other causes of malignancy-related ascites almost always have a negative cytology. Alpha-fetoprotein (AFP) measurement in serum is used in the management of patients with hepatocellular carcinoma (HCC). Measurement of AFP in ascites fluid might be useful, when used in conjunction with cytology, in patients with a history of HCC and in whom a cause of peritoneal fluid accumulation is uncertain.

**Useful For:** An adjunct to cytology to differentiate between malignancy-related ascites and benign causes of ascites formation

**Interpretation:** A peritoneal fluid alpha-fetoprotein (AFP) concentration >6.0 ng/mL is suspicious but not diagnostic of ascites related to hepatocellular carcinoma (HCC). This clinical decision limit cutoff yielded a sensitivity of 58%, specificity of 96% in a study of 137 patients presenting with ascites. AFP concentrations were significantly higher in ascites caused by HCC. Ascites caused by malignancies other than HCC routinely had AFP concentrations <6.0 ng/mL. Therefore, negative results should be interpreted with caution.

**Reference Values:**
An interpretive report will be provided.


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**MAFP1**

**Alpha-Fetoprotein (AFP), Single Marker Screen, Maternal, Serum**

**Clinical Information:** Analytes: Alpha-fetoprotein (AFP) is a fetal protein that is initially produced in the fetal yolk sac and liver. A small amount also is produced by the gastrointestinal tract. By the end of the first trimester, nearly all of the AFP is produced by the fetal liver. The concentration of AFP peaks in fetal serum between 10 to 13 weeks. Fetal AFP diffuses across the placental barrier into the maternal circulation. A small amount also is transported from the amniotic cavity. The AFP concentration in maternal serum rises throughout pregnancy, from the nonpregnancy level of 0.20 ng/mL to about 250 ng/mL at 32 weeks gestation. If the fetus has an open neural tube defect (NTD), AFP is thought to leak directly into the amniotic fluid causing unexpectedly high concentrations of AFP. Subsequently, the AFP reaches the maternal circulation; thus producing elevated serum levels. Other fetal abnormalities such as omphalocele, gastrochisis, congenital renal disease, esophageal atresia, and other fetal distress situations such as threatened abortion and fetal demise also may show AFP elevations. Increased maternal serum AFP values also may be seen in multiple pregnancies and in unaffected singleton pregnancies in which the gestational age has been underestimated. Lower maternal serum AFP values have been associated with an increased risk for genetic conditions such as trisomy 21 (Down syndrome) and trisomy 18 (Edwards syndrome). Risks for these syndrome disorders are only provided with the use of multiple marker screening (QUAD / Quad Screen [Second Trimester] Maternal, Serum). Measurement of maternal serum AFP values is a standard tool used in obstetrical care to identify pregnancies that may have an increased risk for NTD. The screen is performed by measuring AFP in maternal serum and comparing this value to the median AFP value in an unaffected population to obtain a multiple of the median (MoM). The laboratory has established a MoM cutoff of 2.5 MoM, which classifies each screen as either screen-positive or screen-negative. A screen-positive result indicates that the value obtained exceeds the established cutoff. A positive screen does not provide a diagnosis, but indicates that further evaluation should be considered.

**Useful For:** Prenatal screening for open neural tube defect

**Interpretation:** Neural tube defects (NTD): A screen-negative result indicates that the calculated alpha-fetoprotein (AFP) multiple of the median (MoM) falls below the established cutoff of 2.50 MoM.
A negative screen does not guarantee the absence of NTDs. A screen-positive result indicates that the calculated AFP MoM is $> \text{or } =2.50 \text{ MoM}$ or greater, and may indicate an increased risk for open NTDs. The actual risk depends on the level of AFP and the individual's pre-test risk of having a child with NTD based on family history, geographical location, maternal conditions such as diabetes and epilepsy, and use of folate prior to conception. A screen-positive result does not infer a definitive diagnosis of a NTD, but indicates that further evaluation should be considered. Approximately 80% of pregnancies affected with an open NTD have elevated AFP MoM values greater than 2.5. Follow up: Upon receiving maternal serum screening results, all information used in the risk calculation should be reviewed for accuracy (ie., weight, diabetic status, gestational dating). If any information is incorrect the laboratory should be contacted for a recalculation of the estimated risks. Screen-negative results typically do not warrant further evaluation. Ultrasound is recommended to confirm dates for NTD screen-positive results. If ultrasound yields new dates that differ by at least 7 days, a recalculation should be considered. If dates are confirmed, high-resolution ultrasound and amniocentesis (including amniotic fluid AFP and acetylcholinesterase measurements for NTDs) are typically offered.

**Reference Values:**

**NEURAL TUBE DEFECTS**

An AFP multiple of the median (MoM) <2.5 is reported as screen negative.

AFP MoMs $> \text{or } =2.5$ (singleton and twin pregnancies) are reported as screen positive.

An interpretive report will be provided.

**Clinical References:**


**Alpha-Fetoprotein (AFP), Spinal Fluid**

**Clinical Information:** Alpha-fetoprotein (AFP) is an oncofetal glycoprotein, homologous with albumin that is produced both in early fetal life and in tumors arising from midline embryonic structures. AFP is synthesized in the yolk sac, liver, and gastrointestinal track of the fetus. In adults, the liver synthesizes AFP. AFP is not normally expressed in the central nervous system (CNS). AFP levels in liver are increased in hepatomas and hepatocellular and colon carcinomas, as well as in germ-cell tumors arising from the ovaries and nonseminomatous germ-cell tumors of the testes, testicular teratocarcinomas, and primary germ-cell tumors arising within the CNS. The presence of germinomas in the CNS and CNS involvement in metastatic cancer and meningeal carcinomatosis results in increased levels of AFP in cerebrospinal fluid.

**Useful For:**

An adjunct in the diagnosis of central nervous system (CNS) germinomas and meningeal carcinomatosis 
Evaluating germ-cell tumors, including testicular cancer metastatic to the CNS in conjunction with beta-human chorionic gonadotropin measurement(1) 
An adjunct in distinguishing between suprasellar dysgerminomas and craniopharyngiomas 
A supplement to cerebrospinal fluid cytologic analysis

**Interpretation:** Alpha-fetoprotein (AFP) concentrations that exceed the upper end of normal are consistent with the presence of central nervous system germinoma, meningeal carcinomatosis, or metastatic nonseminomatous testicular cancer. AFP is not elevated in the presence of a craniopharyngioma.

**Reference Values:**

$<1.5 \text{ ng/mL}$

Values for alpha-fetoprotein in cerebrospinal fluid have not been formally established for newborns and infants. The available literature indicates that by 2 months of age, levels comparable to adults should be reached. (Ann Clin Biochem 2005;42:24-29)
**Clinical References:**

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**Alpha-Fetoprotein, Amniotic Fluid**

**Clinical Information:** Alpha-fetoprotein (AFP) is a single polypeptide chain glycoprotein with a molecular weight of approximately 70,000 daltons. Synthesis of AFP occurs primarily in the liver and yolk sac of the fetus. It is secreted in fetal serum, reaching a peak at approximately 13 weeks gestation, after which it rapidly declines until about 22 weeks gestation and then gradually declines until term. Transfer of AFP into maternal circulation is accomplished primarily through diffusion across the placenta. Maternal serum AFP levels rise from the normal nonpregnancy level of 0.20 ng/mL to about 250 ng/mL at 32 weeks gestation. If the fetus has an open neural tube defect, AFP is thought to leak directly into the amniotic fluid causing unexpectedly high concentrations of AFP. Other fetal abnormalities such as omphalocle, gastroschisis, congenital renal disease, and esophageal atresia; and other fetal distress situations such as threatened abortion, prematurity, and fetal demise, may also show AFP elevations. Decreased amniotic fluid AFP values may be seen when gestational age has been overestimated.

**Useful For:** Screening for open neural tube defects or other fetal abnormalities Follow-up testing for patients with elevated serum alpha-fetoprotein results or in conjunction with cytogenetic testing

**Interpretation:** A diagnostic alpha-fetoprotein (AFP) cutoff level of 2.0 multiples of median (MoM), followed by acetylcholinesterase (AChE) confirmatory testing on positive results, is capable of detecting 96% of open spina bifida cases with a false-positive rate of only 0.06% in non blood-stained specimens. AChE analysis is an essential confirmatory test for all amniotic fluid specimens with positive AFP results. Normal amniotic fluid does not contain AChE, unless contributed by the fetus as a result of open communication between fetal central nervous system (eg, open neural tube defects), or to a lesser degree, fetal circulation. All amniotic fluid specimens testing positive for AFP will have the AChE test performed. False-positive AChE may occur from a bloody tap, which may cause both elevated AFP and AChE levels.

**Reference Values:**
< or =2.0 multiples of median (MoM)

**Clinical References:** Assessing the Quality of Systems for Alpha-Fetoprotein (AFP) Assays Used in Prenatal Screening and Diagnosis of Open Neural Tube Defects: Approved Guideline. NCCLS I/LA17-A Vol 17. No 5. April 1997

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**Alpha-Fucosidase, Leukocytes**

**Clinical Information:** Fucosidosis is an autosomal recessive lysosomal storage disorder caused by reduced or absent alpha-L-fucosidase enzyme activity. This enzyme is involved in degrading asparagine-linked, fucose-containing complex molecules (oligosaccharides, glycoasparagines) present in cells. Reduced or absent activity of this enzyme results in the abnormal accumulation of these molecules in the tissues and body fluids. Severe and mild subgroups of fucosidosis, designated types I and II, have been described, although recent data suggests individual patients may represent a continuum within a wide spectrum of severity. The more severe type is characterized by infantile onset, rapid psychomotor regression, and severe neurologic deterioration. Additionally, dystososis multiplex and elevated sweat sodium chloride are frequent findings. Death typically occurs within the first decade of life. Those with the milder phenotype express comparatively mild psychomotor and neurologic regression, radiologic signs of dystososis multiplex and skin lesions (angiokeratoma corporis diffusum). Normal sweat salinity, the presence of the skin lesions, and survival into adulthood most readily
distinguish milder from more severe phenotypes. Although the disorder is panethnic, the majority of reported patients with fucosidosis have been from Italy and southwestern United States. To date, about 100 cases have been reported worldwide. An initial diagnostic workup includes a multianalyte or multienzyme screening assay for several oligosaccharidoses, including fucosidosis, in urine, leukocytes, or fibroblasts (OLIGU / Oligosaccharide Screen, Urine; OLIWB / Oligosaccharidoses Screen, Leukocytes or OLITC / Oligosaccharidoses Screen, Fibroblasts). If the screening assay is suggestive of fucosidosis, enzyme analysis of alpha-L-fucosidase can confirm the diagnosis.

**Useful For:** Detection of fucosidosis

**Interpretation:** Values below 0.32 nmol/min/mg protein are consistent with a diagnosis of fucosidosis.

**Reference Values:**
> or =0.32 nmol/min/mg protein

**Clinical References:**

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**FAGPL**

**Alpha-Gal Panel**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal 1 0.35-0.69 Low Positive 2 0.70-3.4 Moderate Positive 3 3.5-17.4 High Positive 4 17.5-49.9 Very High Positive 5 50.0-99.9 Very High Positive 6 > or = 100 Very High Positive

**Reference Values:**
- Beef IgE <0.35 kU/L
- Lamb/Mutton IgE <0.35 kU/L
- Pork IgE <0.35 kU/L
- Galactose-alpha-1,3-galactose (Alph Gal) IgE* <0.35 kU/L

Previous reports (JACI 2009; 123:426-433) have demonstrated that patients with IgE antibodies to galactose-a-1, 3-galactose are at risk for delayed anaphylaxis, angioedema, or urticaria following consumption of beef, pork, or lamb.

* This test was developed and its performance characteristics determined by Viracor Eurofins. It has not been cleared or approved by the FDA.

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**AGABS**

**Alpha-Galactosidase, Blood Spot**

**Clinical Information:** Fabry disease is an X-linked recessive lysosomal storage disorder resulting from deficient activity of the enzyme alpha-galactosidase A (a-Gal A) and the subsequent deposition of glycosylsphingolipids in tissues throughout the body, in particular, the kidney, heart, and brain. More than 150 mutations in the GLA gene have been identified in individuals diagnosed with Fabry disease. Severity and onset of symptoms are dependent on the amount of residual enzyme activity. The classic form of Fabry disease occurs in males who have less than 1% a-Gal A activity. Symptoms usually appear in childhood or adolescence and can include acroparesthesias (pain crises in the extremities), multiple angiokeratomas, reduced or absent sweating, and corneal opacity. In addition, progressive renal involvement leading to end-stage renal disease typically occurs in adulthood followed by cardiovascular and cerebrovascular disease. The estimated incidence is 1 in 40,000 males. Males with residual a-Gal A activity above 1% may present with 1 of 3 variant forms of Fabry disease with onset of symptoms later in
life. These include a renal variant associated with end stage renal disease (ESRD), but without the pain or
skin lesions; a cardiac variant typically presenting in the sixth to eighth decade with left ventricular
hypertrophy, cardiomyopathy, and arrhythmia, and proteinuria, but without ESRD; and a cerebrovascular
variant presenting as stroke or transient ischemic attack. The variant forms of Fabry disease may be
underdiagnosed. Unless irreversible damage has already occurred, treatment with enzyme replacement
therapy (ERT) has led to significant clinical improvement in affected individuals. For this reason, early
diagnosis and treatment are desirable, and, in a few US states, early detection of Fabry disease through
newborn screening has been implemented. Females who are carriers of Fabry disease can have clinical
presentations ranging from asymptomatic to severely affected. Measurement of alpha-Gal A activity is not
generally useful for identifying carriers of Fabry disease, as many of these individuals have normal levels
of alpha-Gal A. Additional studies including molecular genetic analysis of the GLA gene (FABRZ / Fabry
Disease, Full Gene Analysis) are recommended to detect carriers. Reduced or absent a-Gal A in blood
spots, leukocytes (AGA / Alpha-Galactosidase, Leukocytes), or serum (AGAS / Alpha-Galactosidase,
Serum) can indicate a diagnosis of classic or variant Fabry disease. Molecular sequence analysis of the
GLA gene (FABRZ / Fabry Disease, Full Gene Analysis) allows for detection of the disease-causing
mutation. The following algorithms are available in Special Instructions: -Fabry Disease Testing
Algorithm -Fabry Disease: Newborn Screen-Positive Follow-up

Useful For: Evaluation of patients with a clinical presentation suggestive of Fabry disease Follow-up
to an abnormal newborn screen for Fabry disease

Interpretation: In male patients, results less than 1.2 nmol/mL/hour in properly submitted
specimens are consistent with Fabry disease. Normal results (> or =1.2 nmol/mL/hour) are not
consistent with Fabry disease. In female patients, normal results (> or =2.8 nmol/mL/hour) in properly
submitted specimens are typically not consistent with carrier status for Fabry disease; however, enzyme
analysis, in general, is not sufficiently sensitive to detect all carriers. Because a carrier range has not
been established in females, molecular genetic analysis of the GLA gene (FABRZ / Fabry Disease, Full
Gene Analysis) should be considered when alpha-galactosidase A activity is less than 2.9
nmol/mL/hour, or if clinically indicated. Pseudodeficiency results in low measured alpha-galactosidase
A, but is not consistent with Fabry disease; FABRZ / Fabry Disease, Full Gene Analysis should be
performed to resolve the clinical question. See Fabry Disease Testing Algorithm in Special Instructions.

Reference Values:
Males: > or =1.2 nmol/mL/hour
Females: > or =2.8 nmol/mL/hour
An interpretive report will be provided.


AGA 8785

Alpha-Galactosidase, Leukocytes

Clinical Information: Fabry disease is an X-linked lysosomal storage disorder resulting from
deficient activity of the enzyme alpha-galactosidase A (alpha-Gal A) and the subsequent deposition of
glycosylphospholipids in tissues throughout the body, in particular, the kidney, heart, and brain. Fabry
disease is due to mutations within the GLA gene, and more than 630 mutations have been identified in
individuals diagnosed with Fabry disease. Severity and onset of symptoms are dependent on the amount
of residual enzyme activity. The classic form of Fabry disease occurs in males who have less than 1%
alpha-Gal A activity. Symptoms usually appear in childhood or adolescence and can include
acroparesthesias (burning pain in the extremities), gastrointestinal issues, multiple angiokeratomas,
reduced or absent sweating, corneal opacity, and proteinuria. In addition, progressive renal involvement
leading to end-stage renal disease typically occurs in adulthood, followed by cardiovascular and
cerebrovascular disease. The estimated incidence varies from 1 in 3,000 infants detected via newborn screening to 1 in 10,000 males diagnosed after onset of symptoms. Males with residual α-Gal A activity greater than 1% may present with 1 of 3 variant forms of Fabry disease with onset of symptoms later in life: a renal variant associated with end stage renal disease (ESRD) but without the pain or skin lesions; a cardiac variant typically presenting in the sixth to eighth decade with left ventricular hypertrophy, cardiomyopathy and arrhythmia, and proteinuria, but without ESRD; and a cerebrovascular variant presenting as stroke or transient ischemic attack. The variant forms of Fabry disease may be underdiagnosed. Females who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. Measurement of alpha-Gal A activity is not generally useful for identifying carriers of Fabry disease, as many of these individuals have normal levels of alpha-Gal A. Therefore, molecular genetic analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis) is recommended as the most appropriate diagnostic test to detect carriers. Unless irreversible damage has already occurred, treatment with enzyme replacement therapy (ERT) has led to significant clinical improvement in affected individuals. For this reason, early diagnosis and treatment are desirable, and in a few US states early detection of Fabry disease through newborn screening has been implemented. Absent or reduced alpha-Gal A in blood spots, leukocytes (AGA / Alpha-Galactosidase, Leukocytes), or serum (AGAS / Alpha-Galactosidase, Serum) can indicate a diagnosis of classic or variant Fabry disease. Molecular sequence analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis) allows for detection of the disease-causing mutation in males and females. The following algorithms are available in Special Instructions: - Fabry Disease: Newborn Screen-Positive Follow-up - Fabry Disease Testing Algorithm

**Useful For:** Diagnosis of Fabry disease in males Verifying abnormal serum alpha-galactosidase results in males with a clinical presentation suggestive of Fabry disease

**Interpretation:** Deficiency of alpha-galactosidase A (alpha-Gal A) is diagnostic for Fabry disease in males. Urine sediment analysis (CTSA / Ceramide Trihexosides and Sulfatides, Urine) for the accumulating trihexoside substrate is also recommended. Carrier females usually have alpha-galactosidase levels in the normal range; therefore, molecular sequence analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis) is recommended as the appropriate diagnostic test for females.

**Reference Values:**

> or =23.1 nmol/hour/mg protein

An interpretative report will be provided.

Note: Results from this assay do not reflect carrier status because of individual variation of alpha-galactosidase enzyme levels.

**Clinical References:**


**AGAS**

**Alpha-Galactosidase, Serum**

**Clinical Information:** Fabry disease is an X-linked lysosomal storage disorder resulting from deficient activity of the enzyme alpha-galactosidase A (alpha-Gal A) and the subsequent deposition of glycosylsphingolipids in tissues throughout the body; in particular, the kidney, heart, and brain. Fabry disease is caused by mutations within the GLA gene, and more than 630 mutations have been identified in individuals diagnosed with Fabry disease. Severity and onset of symptoms are dependent on the amount...
of residual enzyme activity. The classic form of Fabry disease occurs in males who have less than 1% alpha-Gal A activity. Symptoms usually appear in childhood or adolescence and can include acroparesthesias (burning pain in the extremities), gastrointestinal issues, multiple angiokeratomas, reduced or absent sweating, corneal opacity, and proteinuria. In addition, progressive renal involvement leading to end-stage renal disease typically occurs in adulthood, followed by cardiovascular and cerebrovascular disease. The estimated incidence varies from 1 in 3,000 infants detected via newborn screening to 1 in 10,000 males diagnosed after onset of symptoms. Males with residual a-Gal A activity greater than 1% may present with 1 of 3 variant forms of Fabry disease with onset of symptoms later in life: a renal variant associated with end stage renal disease (ESRD) but without the pain or skin lesions; a cardiac variant typically presenting in the sixth to eighth decade with left ventricular hypertrophy, cardiomyopathy and arrhythmia, and proteinuria, but without ESRD; and a cerebrovascular variant presenting as stroke or transient ischemic attack. The variant forms of Fabry disease may be underdiagnosed. Females who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. Measurement of alpha-Gal A activity is not generally useful for identifying carriers of Fabry disease, as many of these individuals have normal levels of alpha-Gal A. Therefore, molecular genetic analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis) is recommended to detect carriers. Unless irreversible damage has already occurred, treatment with enzyme replacement therapy (ERT) has led to significant clinical improvement in affected individuals. For this reason, early diagnosis and treatment are desirable, and in a few US states early detection of Fabry disease through newborn screening has been implemented. Absent or reduced alpha-Gal A in blood spots, leukocytes (AGA / Alpha-Galactosidase, Leukocytes), or serum (AGAS / Alpha-Galactosidase, Serum) can indicate a diagnosis of classic or variant Fabry disease. Molecular sequence analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis) allows for detection of the disease-causing mutation in males and females. See Fabry Disease Testing Algorithm and Fabry Disease: Newborn Screen-Positive Follow-up in Special Instructions.

**Useful For:** Diagnosis of Fabry disease in males Preferred screening test (serum) for Fabry disease

**Interpretation:** Deficiency (<0.016 U/L) of alpha-galactosidase in properly submitted specimens is diagnostic for Fabry disease in males. If concerned about specimen integrity, recheck using leukocyte testing (AGA / Alpha-Galactosidase, Leukocytes). Urine sediment analysis (CTSA / Ceramide Trihexosides and Sulfatides, Urine) for the accumulating trihexoside substrate is also recommended. Carrier females usually have alpha-galactosidase levels in the normal range; therefore, molecular sequence analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis) is recommended as the appropriate diagnostic test for females.

**Reference Values:**
0.074-0.457 U/L

Note: Results from this assay are not useful for carrier determination. Carriers usually have levels in the normal range.

**Clinical References:**

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**ATHL 58114 Alpha-Globin Gene Analysis**

**Reference Values:**

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
**Alpha-Globin Gene Analysis**

**Clinical Information:** The thalassemias are a group of inherited conditions characterized by decreased synthesis of one or more of the globin chains, resulting in an imbalance in the relative amounts of the alpha and beta chains. The excess normal chains precipitate in the cell, damaging the membrane and leading to premature red blood cell destruction. Additionally, the defect in hemoglobin synthesis produces a hypochromic, microcytic anemia. The frequency of thalassemia is due to the protective advantage against malaria that it gives carriers. Consequently, thalassemias are prevalent in populations from equatorial regions in the world where malaria is endemic. Alpha-thalassemia is caused by decreased synthesis of alpha-globin chains. Four alpha-globin genes are normally present (2 on each chromosome 16). One, 2, 3, or 4 alpha-globin genes may be deleted or, less commonly, contain mutations. Deletions account for approximately 90% of disease-causing alleles in alpha thalassemia. Phenotypically, these deletions result in 4 categories of disease expression: -Deletion of 1 alpha-chain: Silent carrier state, with a normal phenotype -Deletion of 2 alpha-chains: Alpha-thalassemia trait (alpha-1 thalassemia), with mild hematologic changes but no major clinical difficulties -Deletion of 3 alpha-chains: Hemoglobin H disease, which is extremely variable but usually includes anemia due to hemolysis, jaundice, and hepatosplenomegaly -Deletion of all 4 alpha-chains: Hemoglobin Bart, with hydrops fetalis and almost invariably in utero demise Less frequently, alpha-thalassemia results from single point mutations. The most common nondeletion mutation is hemoglobin Constant Spring (HbCS) (HBA2: c.427T >C). Point mutations other than HbCS and alpha-thalassemia Saudi are not detected by this assay. Alpha-thalassemia occurs in all ethnic groups but is especially common individuals of Southeast Asian and African ancestry. It is also frequent in individuals of Mediterranean ancestry. The carrier frequency is estimated to be 1 in 20 for Southeast Asians, 1 in 30 for African Americans, and 1 in 30 to 1 in 50 for individuals of Mediterranean ancestry. Both deletional and nondeletional (caused by point mutations) forms of alpha-thalassemia are found in individuals with Mediterranean ancestry. Deletions in cis (deletions on the same chromosome) are rare in African or Mediterranean populations, but are prevalent in Asian populations. Couples in which both partners carry deletions in cis are at risk of having a child with the fatal hemoglobin Bart hydrops fetalis syndrome.

**Useful For:** Diagnosis of alpha-thalassemia Prenatal diagnosis of deletional alpha-thalassemia Carrier screening for individuals from high-risk populations for alpha-thalassemia

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Alpha-L-Iduronidase, Blood**

**Clinical Information:** The mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate, also known as glycosaminoglycans (GAG). Accumulation of GAGs in lysosomes interferes with normal functioning of cells, tissues, and organs. There are 11 known disorders that involve the accumulation of GAGs. MPS disorders involve multiple organ systems characterized by coarse facial features, cardiac abnormalities, organomegaly, intellectual disabilities, short stature, and skeletal abnormalities. Mucopolysaccharidosis I (MPS I) is an autosomal recessive disorder caused by a reduced or absent activity of the enzyme alpha-L-iduronidase due to...
mutations in the IDUA gene. More than 100 mutations have been reported in individuals with MPS I. Deficiency of alpha-L-iduronidase can result in a wide range of phenotypes categorized into 3 syndromes: Hurler syndrome (MPS IH), Scheie syndrome (MPS IS), and Hurler-Scheie syndrome (MPS IH/S). Because these syndromes cannot be distinguished biochemically, they are also referred to as MPS I and attenuated MPS I. Clinical features and severity of symptoms of MPS I are variable, ranging from severe disease to an attenuated form that generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, progressive dysostosis multiplex, hepatosplenomegaly, corneal clouding, hearing loss, intellectual disabilities or learning difficulties, and cardiac valvular disease. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. A diagnostic workup in an individual with MPS I typically demonstrates elevated levels of urinary GAG (MPSQN / Mucopolysaccharides [MPS], Quantitative, Urine) and increased amounts of both dermatan and heparan sulfate being detected (MPSSC / Mucopolysaccharides [MPS] Screen, Urine). Reduced or absent activity of alpha L-iduronidase can confirm a diagnosis of MPS I; however, enzymatic testing is not reliable for carrier detection. Molecular sequence analysis of the IDUA gene allows for detection of the disease-causing mutation in affected patients and subsequent carrier detection in relatives. To date, a clear genotype-phenotype correlation has not been established.

Useful For: Diagnosis of mucopolysaccharidosis I, Hurler, Scheie, and Hurler-Scheie syndromes in whole blood specimens

Interpretation: Specimens with results below 1.0 nmol/hour/mL in properly submitted specimens are consistent with alpha-L-iduronidase deficiency (mucopolysaccharidosis I). Further differentiation between Hurler, Scheie, and Hurler-Scheie is dependent upon the clinical findings. Normal results (> or =1.0 nmol/h/mL) are not consistent with alpha-L-iduronidase deficiency.

Reference Values:
> or =1.0 nmol/hour/mL
An interpretive report will be provided.

Clinical References:
MPS I are variable, ranging from severe disease to an attenuated form that generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, progressive dysostosis multiplex, hepatosplenomegaly, corneal clouding, hearing loss, intellectual disabilities or learning difficulties, and cardiac valvular disease. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. A diagnostic workup in an individual with MPS I typically demonstrates elevated levels of urinary GAG (MPSQN / Mucopolysaccharides [MPS], Quantitative, Urine) and increased amounts of both dermatan and heparan sulfate detected on thin-layer chromatography (MPSSC / Mucopolysaccharides [MPS] Screen, Urine). Reduced or absent activity of alpha-L-iduronidase in blood spots, fibroblasts (IDST / Alpha-L-Iduronidase, Fibroblasts), leukocytes, or whole blood (IDSWB / Alpha-L-Iduronidase, Blood) can confirm a diagnosis of MPS I; however, enzymatic testing is not reliable for carrier detection. Molecular sequence analysis of the IDUA gene allows for detection of the disease-causing mutation in affected patients and subsequent carrier detection in relatives. To date, a clear genotype-phenotype correlation has not been established.

**Useful For:** Diagnosis of mucopolysaccharidoses I, Hurler, Scheie, and Hurler-Scheie syndromes using dried blood spot specimens

**Interpretation:** Specimens with results below 1.0 nmol/hour/mL in properly submitted specimens are consistent with alpha-L-iduronidase deficiency (mucopolysaccharidosis I). Further differentiation between Hurler, Scheie, and Hurler-Scheie is dependent on the clinical findings. Normal results (> or = 1.0 nmol/hour/mL) are not consistent with alpha-L-iduronidase deficiency.

**Reference Values:**
> or = 1.0 nmol/h/mL
An interpretive report will be provided.

**Clinical References:**

**ALFA**

**Alpha-Lactoalbumin, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of
allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


**MANN 62511**

**Alpha-Mannosidase, Leukocytes**

**Clinical Information:** Alpha-mannosidosis is an autosomal recessive lysosomal storage disorder caused by reduced or absent acid alpha-mannosidase enzyme activity. This enzyme is involved in glycoprotein catabolism, with absent or reduced activity resulting in the accumulation of undigested mannose-containing complex oligosaccharides in the lysosomes, disrupting the normal functioning of cells. Clinical features and severity of symptoms are widely variable within alpha-mannosidosis but, in general, the disorder is characterized by skeletal abnormalities, immune deficiency, hearing impairment, and mental retardation. Three clinical subtypes of the disorder have been described and vary with respect to age of onset and clinical presentation. Type 1 is generally classified by a mild presentation and slow progression with onset after 10 years of age and absence of skeletal abnormalities. Type 2 is generally a more moderate form with slow progression and onset prior to 10 years of age with skeletal abnormalities and myopathy. Type 3 is the most severe form with onset in early infancy, skeletal abnormalities (dysostosis multiplex), and severe central nervous system involvement. Although treatment is mostly supportive and aimed at preventing complications, hematopoietic stem cell transplant has been reported to be a feasible therapeutic option. The incidence of alpha-mannosidosis is estimated at 1 in 500,000 live births. An initial diagnostic workup may include a multi-enzyme screening assay for several oligosaccharidoses, including mannosidosis in leukocytes or fibroblasts (OLIGU / Oligosaccharide Screen, Urine; OLIWB / Oligosaccharidoses Screen, Leukocytes; or OLITC / Oligosaccharidoses Screen, Fibroblasts). If the screening assay is suggestive of alpha-mannosidosis, enzyme analysis of acid alpha-mannosidase can confirm the diagnosis.

**Useful For:** Diagnosis of alpha-mannosidosis

**Interpretation:** Values below 0.54 nmol/min/mg protein are consistent with a diagnosis of alpha-mannosidosis.

**Reference Values:** > or =0.54 nmol/min/mg protein

**Alpha-N-Acetylgalactosaminidase, Serum**

**Clinical Information:** The mucopolysaccharidoses (MPS) are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans GAG). Accumulation of GAG in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in MPS disorders. Sanfilippo syndrome (MPS type III) is an autosomal recessive MPS with 4 recognized types (A-D). Each type is caused by a deficiency in 1 of 4 enzymes involved in the degradation of heparan sulfate resulting in its lysosomal accumulation. Though biochemically different, the clinical presentation of all types is indistinguishable. Sanfilippo syndrome is characterized by severe central nervous system (CNS) degeneration, but other symptoms seen in MPS, such as coarse facial features and skeletal involvement, tend to be milder. Onset of clinical features usually occurs between 2 and 6 years in a child who previously appeared normal. The presenting symptoms are most commonly developmental delay and severe behavioral problems. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by age 20, although individuals with an attenuated phenotype may have a longer life expectancy and remain functional into their third and fourth decades. Sanfilippo syndrome type B is due to the absence of the enzyme N-acetyl-alpha-D-glucosaminidase (alpha-hexosaminidase), caused by mutations in the NAGLU gene. Affected individuals demonstrate elevations of heparan sulfate in urine. Diagnostic sequencing of the NAGLU gene (MP3BZ / Mucopolysaccharidosis IIIB, Full Gene Analysis) and deletion/duplication studies are available for patients with an enzyme deficiency. Patients with Mucolipidosis II/III (I-cell disease) may demonstrate elevations of alpha-N-acetylgalactosaminidase in addition to abnormalities of other hydrolases. I-cell disease is an autosomal recessive lysosomal storage disorder resulting in impaired transport and phosphorylation of newly synthesized lysosomal proteins to the lysosome due to deficiency of N-acetylgalactosamine 1-phosphotransferase (GlcNAc). Characteristic clinical features include short stature, skeletal and cardiac abnormalities, and developmental delay. Measurement of alpha-N-acetylgalactosaminidase activity is not the preferred diagnostic test for I-cell disease but may be included in the testing strategy.

**Useful For:** Preferred assay for diagnosis of Sanfilippo syndrome type B (mucopolysaccharidoses type IIIB)

**Interpretation:** Deficiency of alpha-N-acetylgalactosaminidase is diagnostic for Sanfilippo syndrome type B.

**Reference Values:**

0.09-0.58 U/L

**Clinical References:**

**Alpha-Subunit Pituitary Tumor Marker, Serum**

**Clinical Information:** The 3 human pituitary glycoprotein hormones: luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyrotropin (TSH), and the placenta-derived choriionic gonadotropin (hCG), are closely related tropic hormones. They signal through G-protein-coupled receptors, regulating the hormonal activity of their respective endocrine target tissues. Each is composed of an alpha- and a beta-subunit, coupled by strong noncovalent bonds. The alpha-subunits of all 4 hormones are essentially identical (92 amino acids; molecular weight [MW] of the "naked" protein:10,205 Da), being transcribed from the same gene and showing only variability in glycosylation (MW of the glycosylated proteins:13,000-18,000 Da). The alpha-subunits are essential for receptor transactivation. By contrast, all the different beta-subunits are transcribed from separate genes, show less homology, and convey the receptor specificity of the dimeric hormones. Under physiological conditions, alpha- and beta-chain synthesis and secretions are tightly coupled, and only small amounts of monomeric subunits are secreted. However, under certain conditions, coordinated production of intact glycoprotein hormones may be disturbed and disproportionate quantities of free alpha-subunits are secreted. In particular, some pituitary adenomas may overproduce alpha-subunits. Although most commonly associated with gonadotroph- or thyrotroph-derived tumors, alpha-subunit secretion has also been observed in corticotroph, lactotroph, and somatotroph pituitary adenomas. Overall, depending on cell type and tumor size, between 5% to 30% of pituitary adenomas will produce sufficient free alpha-subunits to result in elevated serum levels, which usually fall with successful treatment.

Stimulation testing with hypothalamic releasing factors (eg, gonadotropin releasing hormone [GnRH] or thyrotropin-releasing hormone [TRH]) may result in further elevations, disproportionate to those seen in individuals without tumors. Measurement of free alpha-subunit after GnRH-stimulation testing can also be useful in the differential diagnosis of constitutional delay of puberty (CDP) versus hypogonadotropic hypogonadism (HH). CDP is a benign, often familial, condition in which puberty onset is significantly delayed, but eventually occurs, and then proceeds normally. By contrast, HH represents a disease state characterized by lack of gonadotropin production. Its causes are varied, including hypothalamic and pituitary inflammatory or neoplastic disorders, a range of specific genetic abnormalities, as well as unknown causes. In children, HH results in complete failure to enter puberty without medical intervention. In children with CDP, in normal pubertal children, in normal adults and, to a lesser degree, in normal prepubertal children, GnRH administration results in increased serum LH, FSH, and alpha-subunit levels. This response is greatly attenuated in patients with HH, particularly with regard to the post-GnRH rise in alpha-subunit concentrations.

**Useful For:**
- Adjunct in the diagnosis of pituitary tumors
- As part of the follow-up of treated pituitary tumor patients
- Differential diagnosis of thyrotropin-secreting pituitary tumor versus thyroid hormone resistance
- Differential diagnosis of constitutional delay of puberty versus hypogonadotropic hypogonadism

**Interpretation:** In the case of pituitary adenomas that do not produce significant amounts of intact tropic hormones, diagnostic differentiation between sellar- and tumors of nonpituitary origin (eg, meningiomas or craniopharyngiomas) can be difficult. In addition, if such nonsecreting adenomas are very small, then they can be difficult to distinguish from physiological pituitary enlargements. In a proportion of these cases, free alpha-subunit may be elevated, aiding in diagnosis. Overall, 5% to 30% of pituitary adenomas produce measurable elevation in serum free alpha-subunit concentrations. There is also evidence that an exuberant free alpha-subunit response to thyrotropin-releasing hormone (TRH) administration may occur in some pituitary adenoma patients that do not have elevated baseline free alpha-subunit levels. A more than 2-fold increase in free alpha-subunit serum concentrations at 30 to 60 minutes following intravenous administration of 500 mcg of TRH is generally considered abnormal, but some investigators consider any increase of serum free alpha-subunit that exceeds the reference range as abnormal. TRH testing is not performed in the laboratory, but in specialized clinical testing units under the supervision of a physician. In pituitary tumors patients with pre-treatment elevations of serum free alpha-subunit, successful treatment is associated with a reduction of serum free alpha-subunit levels. Failure to lower levels into the normal reference range may indicate incomplete cure, and secondary rises in serum free alpha-subunit levels can indicate tumor recurrence. Small thyrotropin
TSH-secreting pituitary tumors are difficult to distinguish from thyroid hormone resistance. Both types of patients may appear clinically euthyroid or mildly hyperthyroid and may have mild-to-modest elevations in peripheral thyroid hormone levels along with inappropriately (for the thyroid hormone level) detectable TSH, or mildly-to-modestly elevated TSH. Elevated serum free alpha-subunit levels in such patients suggest a TSH secreting tumor, but mutation screening of the thyroid hormone receptor gene may be necessary for a definitive diagnosis. Constitutional delay of puberty (CDP), is a benign, often familial condition, in which puberty onset is significantly delayed, but eventually occurs and then proceeds normally. By contrast, hypogonadotrophic hypogonadism (HH) represents a disease state characterized by lack of gonadotropin production. Its causes are varied, ranging from idiopathic over specific genetic abnormalities to hypothalamic and pituitary inflammatory or neoplastic disorders. In children, it results in complete failure to enter puberty without medical intervention. CDP and HH can be extremely difficult to distinguish from each other. Intravenous administration of 100 mcg gonadotropin releasing hormone (GnRH) results in much more substantial rise in free alpha-subunit levels in CDP patients, compared with HH patients. A greater than 6-fold rise at 30 or 60 minutes post-injection is seen in more than 75% of CDP patients, while a less than 2-fold rise appears diagnostic of HH. Increments between 2-fold and 6-fold are nondiagnostic. GnRH testing is not performed in the laboratory, but in specialized clinical testing units under the supervision of a physician.

**Reference Values:**

**PEDIATRIC**
- < or =5 days: < or =50 ng/mL
- 6 days-12 weeks: < or =10 ng/mL
- 3 months-17 years: < or =1.2 ng/mL
- Tanner II-IV*: < or =1.2 ng/mL

**ADULTS**
- Males: < or =0.5 ng/mL
- Premenopausal females: < or =1.2 ng/mL
- Postmenopausal females: < or =1.8 ng/mL

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.

**Clinical References:**

**Alpha/Beta Crystallin IHC, Technical Component Only**

**Clinical Information:** Alpha-beta crystallin is a lens protein and a member of the superfamily of small heat shock proteins. It is expressed in a variety of tissues such as skeletal muscle, cardiac muscle, smooth muscle, renal tubular epithelium, Schwann cells, glial cells, thyroid epithelium, colonic epithelium, and stratified squamous epithelium. It is also found in ubiquitinated intermediate filament inclusion bodies, such as Lewy bodies (neurofilaments), Rosenthal fibers (glial filaments), and Mallory bodies (cytokeratins) present in certain disease states.
**Useful For:** Characterization of neuroectodermal tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**ALPRT 70593**

**Alport (Collagen IV Alpha 5 and Alpha 2) Immunofluorescent Stain, Renal**

**Clinical Information:** Alport syndrome is a hereditary disease of basement membrane collagen type IV. Mutations in collagen IV alpha genes cause characteristic abnormal immunofluorescence staining patterns within the glomerular basement membrane. Alport syndrome is characterized by hematuria, proteinuria, progressive renal failure, and high-tone sensorineural hearing loss.

**Useful For:** Assisting in the diagnosis of hereditary nephritis (Alport syndrome)

**Interpretation:** This test, (when not accompanied by a pathology consultation request) will be reported as: 1) normal pattern, 2) consistent with X-linked hereditary nephritis, or 3) consistent with autosomal hereditary nephritis. If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test and send the corresponding renal pathology light microscopy and immunofluorescence (IF) slides (or IF images on a CD), electron microscopy images (prints or CD), and the pathology report.

**Reference Values:**
Reporting of immunofluorescent (IF) double staining for alpha 2 and alpha 5 chains of type IV collagen on kidney biopsies:

1) Normal pattern of staining (ie, preserved linear alpha 5 staining of glomerular basement membranes, Bowman capsule, and distal tubular basement membranes). This pattern of staining is seen in normal individuals and patients with thin glomerular basement membrane disease but does not exclude the diagnosis of hereditary nephritis/Alport syndrome.

2) Consistent with X-linked hereditary nephritis (Alport syndrome). There is global or segmental loss of alpha 5 staining of glomerular basement membranes, Bowman capsule, and distal tubular basement membranes. This pattern of loss of staining is usually due to mutations in the COL4A5 gene on the X chromosome.

3) Consistent with autosomal hereditary nephritis (Alport syndrome). There is global or segmental loss of alpha 5 staining of glomerular basement membranes but preserved alpha 5 staining of Bowman capsule and distal tubular basement membranes. This pattern of loss of staining is usually due to mutations in the COL4A3 or COL4A4 genes on chromosome 2.

4) No interpretation can be reported if the specimen contains no intact glomeruli.
Reporting of IF double staining for alpha 2 and alpha 5 chains of type IV collagen on skin biopsies:

1) Normal pattern of staining (ie, preserved linear alpha 5 staining of epidermal basement membranes). This pattern of staining is seen in normal individuals and patients with thin glomerular basement membrane disease but does not exclude the diagnosis of hereditary nephritis/Alport syndrome.

2) Consistent with X-linked hereditary nephritis (Alport syndrome): There is global or segmental loss of alpha 5 staining of epidermal basement membranes. This pattern of loss of staining is usually due to mutations in the COL4A5 gene on the X chromosome.

3) No interpretation can be reported if the biopsy contains no epidermis.

Notes:

1) Approximately one-third of patients with established hereditary nephritis based on typical ultrastructural findings and family history show loss of glomerular basement membrane or epidermal basement membrane staining for the alpha 5 chain of type IV collagen. Therefore, a normal staining pattern does not exclude the diagnosis of hereditary nephritis.

2) In patients with hereditary nephritis, preserved alpha 5 staining indicates small mutations (eg, missense, splice site) and is generally associated with a better renal outcome, while loss of alpha 5 staining indicates larger mutations (eg, deletion, nonsense, frame-shift) and a worse renal outcome.

3) Because alpha 3 and alpha 4 chains of type IV collagen are not expressed in the epidermal basement membranes, patients with autosomal hereditary nephritis have preserved staining for alpha 5 on epidermal basement membranes and, therefore, skin biopsy cannot exclude autosomal hereditary nephritis.

Clinical References:


Alprazolam (Xanax)

Reference Values:

5 – 25 ng/mL

Reporting Limit: 2.0 ng/mL

Alternaria tenuis, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm
sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of
allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with
the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>Interpretation</th>
<th>kU/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
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<tr>
<td>1</td>
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<tr>
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<tr>
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<td>3.50-17.4</td>
<td>Positive</td>
</tr>
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<td>4</td>
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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Clinical References:** Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and
Management by Laboratory Methods. 21st edition. Edited by RA McPherson, MR Pincus. WB

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**Aluminum, 24 Hour, Urine**

**Clinical Information:** Under normal physiologic conditions, the usual daily dietary intake of
aluminum (5-10 mg) is completely eliminated. Excretion is accomplished by avid filtration of aluminum
from the blood by the glomeruli of the kidney. Patients in renal failure (RF) lose the ability to clear
aluminum and are candidates for aluminum toxicity. Many factors increase the incidence of aluminum
toxicity in RF patients: -Aluminum-laden dialysis water can expose dialysis patients to aluminum.
-Aluminum-laden albumin can expose patients to an aluminum burden they cannot eliminate. -The
dialysis process is not highly effective at eliminating aluminum. -Aluminum-based phosphate binder
gels are administered orally to minimize phosphate accumulation; a small fraction of this aluminum
may be absorbed and accumulated. If it is not removed by renal filtration, aluminum accumulates in the
blood where it binds to proteins such as albumin and is rapidly distributed through the body. Aluminum
overload leads to accumulation of aluminum at 2 sites: brain and bone. Brain deposition has been
implicated as a cause of dialysis dementia. In bone, aluminum replaces calcium at the mineralization
front, disrupting normal osteoid formation. Urine aluminum concentrations are likely to be increased
above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by
Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium.
This list of products is incomplete, and these products change occasionally; see prosthesis product
information for each device for composition details.

**Useful For:** Monitoring aluminum exposure Monitoring metallic prosthetic implant wear

**Interpretation:** Daily excretion less than 10 mcg/24 hours indicates exposure to excessive amounts
of aluminum. In renal failure, the ability of the kidney to excrete aluminum decreases, while the
exposure to aluminum increases (aluminum-laden dialysis water, aluminum-laden albumin, and
aluminum-laden phosphate binders). Patients receiving chelation therapy with desferrioxamine (for
iron- or aluminum-overload states) also excrete considerably more aluminum in their urine than normal.
Prosthesis wear is known to result in increased circulating concentration of metal ions.(1,2) Modest
increase (10-20 mcg/24 hours) in urine aluminum concentration is likely to be associated with a
prosthetic device in good condition. Urine concentrations above 50 mcg/24 hours in a patient with an
aluminum-based implant, not undergoing dialysis, suggests significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

**Reference Values:**
0-17 years: not established
> or = 18 years: <10 mcg/24h

**Clinical References:**

**Aluminum, Serum**

**Clinical Information:** Under normal physiologic conditions, the usual daily dietary intake of aluminum (5-10 mg) is completely eliminated. Excretion is accomplished by avid filtration of aluminum from the blood by the glomeruli of the kidney. Patients in renal failure (RF) lose the ability to clear aluminum and are candidates for aluminum toxicity. Many factors increase the incidence of aluminum toxicity in patients in RF: -Aluminum-laden dialysis water can expose dialysis patients to aluminum. -Aluminum-laden albumin can expose patients to an aluminum burden they cannot eliminate. -The dialysis process is not highly effective at eliminating aluminum. -Aluminum-based phosphate binder gels are administered orally to minimize phosphate accumulation; a small fraction of this aluminum may be absorbed and accumulated. If it is not removed by renal filtration, aluminum accumulates in the blood where it binds to proteins such as albumin and is rapidly distributed through the body. Aluminum overload leads to accumulation of aluminum at 2 sites: brain and bone. Brain deposition has been implicated as a cause of dialysis dementia. In bone, aluminum replaces calcium at the mineralization front, disrupting normal osteoid formation. Deposition of aluminum in bone also interrupts normal calcium exchange. The calcium in bone becomes unavailable for resorption back into blood under the physiologic control of parathyroid hormone (PTH) and results in secondary hyperparathyroidism. While PTH is typically quite elevated in RF, 2 different processes may occur: 1) High-turnover bone disease associated with high PTH (>150 pg/mL) and relatively low aluminum (<20 ng/mL), or 2) low-turnover bone disease with lower PTH (<50 pg/mL) and high aluminum (>60 ng/mL). Low-turnover bone disease indicates aluminum intoxication. Serum aluminum concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside, typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Preferred monitoring for aluminum toxicity in patients undergoing dialysis Preferred test for routine aluminum screening Monitoring metallic prosthetic implant wear

**Interpretation:** Patients in renal failure not receiving dialysis therapy invariably have serum aluminum levels above the 60 ng/mL range. McCarthy(1) and Hernandez(2) describe a biochemical profile that is characteristic of aluminum overload disease in dialysis patients: -Patients in renal failure with no signs or symptoms of osteomalacia or encephalopathy usually had serum aluminum below 20 ng/mL and parathyroid hormone (PTH) concentrations above 150 pg/mL, which is typical of secondary hyperparathyroidism. -Patients with signs and symptoms of osteomalacia or encephalopathy had serum aluminum above 60 ng/mL and PTH concentrations below 50 pg/mL (PTH above the reference range, but low for secondary hyperparathyroidism). -Patients who had serum aluminum above 60 ng/mL and below 100 ng/mL were identified as candidates for later onset of aluminum-overload disease that required aggressive efforts to reduce their daily aluminum exposure. This was done by switching them from aluminum-containing phosphate binders to calcium-containing phosphate binders, by ensuring that their dialysis water had less than 10 ng/mL of aluminum, and ensuring the albumin used during postdialysis therapy was aluminum free. Prosthesis wear is known to result in increased circulating concentration of metal ions. (3) Modest increase (6-10 ng/mL) in serum aluminum concentration is likely to be associated
with a prosthetic device in good condition. Serum concentrations above 10 ng/mL in a patient with an aluminum-based implant not undergoing dialysis suggest significant prosthesis wear. Increased serum trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

**Reference Values:**
0-6 ng/mL (all ages)
<60 ng/mL (dialysis patients-all ages)

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.

**Clinical References:**

**Aluminum/Creatinine Ratio, Random, Urine**

**Clinical Information:** Under normal physiologic conditions, the usual daily dietary intake of aluminum (5-10 mg) is completely eliminated. Excretion is accomplished by avid filtration of aluminum from the blood by the glomeruli of the kidney. Patients in renal failure (RF) lose the ability to clear aluminum and are candidates for aluminum toxicity. Many factors increase the incidence of aluminum toxicity in RF patients:
- Aluminum-laden dialysis water can expose dialysis patients to aluminum.
- Aluminum-laden albumin can expose patients to an aluminum burden they cannot eliminate.
- The dialysis process is not highly effective at eliminating aluminum. -Aluminum-based phosphate binder gels are administered orally to minimize phosphate accumulation; a small fraction of this aluminum may be absorbed and accumulated. If it is not removed by renal filtration, aluminum accumulates in the blood where it binds to proteins such as albumin and is rapidly distributed through the body. Aluminum overload leads to accumulation of aluminum at 2 sites: brain and bone. Brain deposition has been implicated as a cause of dialysis dementia. In bone, aluminum replaces calcium at the mineralization front, disrupting normal osteoid formation. Urine aluminum concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Monitoring aluminum exposure when a 24-hour urine cannot be collected Monitoring metallic prosthetic implant wear when a 24-hour urine cannot be collected

**Interpretation:** Daily excretion more than 10 mcg/24 hours indicates exposure to aluminum. Prosthesis wear is known to result in increased circulating concentration of metal ions.(1) Modest increase (10-20 mcg/24 hours) in urine aluminum concentration is likely to be associated with a prosthetic device in good condition. Urine concentrations more than 50 mcg/24 hours in a patient with an aluminum-based implant, not undergoing dialysis, suggest significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure. In renal failure, the ability of the kidney to excrete aluminum decreases, while the exposure to aluminum increases (aluminum-laden dialysis water, aluminum-laden albumin, and aluminum-laden phosphate binders). Patients receiving chelation therapy with desferrioxamine (for iron- or aluminum-overload states) also excrete considerably more aluminum in their urine than normal.

**Reference Values:**
0-17 years: not established
> or =18 years: <14 mcg/g Creatinine

Alveolar Rhabdomyosarcoma (ARMS), 13q14 (FOXO1 or FKHR) Rearrangement, FISH, Tissue

Clinical Information: Rhabdomyosarcomas are a heterogeneous group of malignant tumors showing skeletal muscle differentiation. They can be divided into 3 subtypes: alveolar, embryonal, and pleomorphic. The rarer alveolar rhabdomyosarcomas (ARMS) are seen in older children, are more likely to occur in limbs, and are associated with higher stage disease and an unfavorable prognosis. The alveolar form consists of 2 variants; classic and solid. The classic form is characterized by small round cells with dark hyperchromatic nuclei containing distinct nucleoli, held together by strands of intercellular collagen, thereby creating a cellular architecture resembling the alveolar spaces of the lungs. The solid form is characterized by a similar cellular morphology but without the formation of alveolar spaces. ARMS are also members of the small round cell tumor group that includes synovial sarcoma, lymphoma, Wilms tumor, Ewing sarcoma, and desmoplastic small round cell tumor. Most cases of ARMS (75%) are associated with a t(2;13)(q35;q14), where a chimeric gene is formed from the rearrangement of the PAX3 gene on chromosome 2 and the FOXO1(FKHR) gene on chromosome 13. A small subset of ARMS patients (10%) are associated with a variant translocation, t(1;13)(q36;q14), involving the PAX7 gene of chromosome 1 and the FOXO1 gene. Detection of these transcripts by RT-PCR (ARMS / Alveolar Rhabdomyosarcoma by Reverse Transciptase PCR [RT-PCR]), which allows specific identification of the t(2;13) and t(1;13), has greatly facilitated the diagnosis of ARMS tumors. FISH analysis (using the FOXO1 probe) adds the ability to detect variant FOXO1 rearrangements not detectible by PCR, and will often yield results when the quality of the available RNA is poor or the PCR results are equivocal.

Useful For: Supporting the diagnosis of alveolar rhabdomyosarcomas (ARMS) when used in conjunction with an anatomic pathology consultation Aiding in the diagnosis of ARMS when reverse transcriptase-PCR results are equivocal or do not support the clinical picture

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the FOXO1 FISH probe. A positive result suggests rearrangement of the FOXO1 gene region at 13q14 and is consistent with a subset of alveolar rhabdomyosarcomas (ARMS). A negative result suggests FOXO1 gene rearrangement is not present, but does not exclude the diagnosis of alveolar rhabdomyosarcomas (ARMS).

Reference Values: An interpretive report will be provided.

Clinical Information: Alveolar rhabdomyosarcoma (ARMS) is a member of the family of rhabdomyosarcomas (tumors composed of cells showing muscle differentiation) that also includes embryonal, botryoid, spindle cell, and pleomorphic types. (1) Alveolar rhabdomyosarcomas include the classical and solid patterns. (1) ARMS is also a member the small round-cell tumor group that includes synovial sarcoma, lymphoma, Wilms tumor, Ewing sarcoma, and desmoplastic small round-cell tumor. While treatment and prognosis depend on establishing the correct diagnosis, the diagnosis of sarcomas that form the small-round-cell tumor group can be very difficult by light microscopic examination alone, especially true when only small-needle biopsy specimens are available for examination. The use of immunohistochemical stains (eg, desmin, actin, and the nuclear transcription factor markers MyoD and myogenin) are useful in separating rhabdomyosarcomas from other small-round-cell tumors, but do not always distinguish the various subtypes of rhabdomyosarcomas. Expertise in soft tissue and bone pathology are often needed. Studies have shown that some sarcomas have specific recurrent chromosomal translocations. These translocations produce highly specific gene fusions that help define and characterize subtypes of sarcomas and are useful in the diagnosis of these lesions. (1-4) Most cases of ARMS have a t(2;13)(q35;q14) reciprocal translocation. This rearrangement juxtaposes 5' portions of the PAX3 gene on chromosome 2 with 3' portion of the FOXO1 gene on chromosome 13 resulting in a chimeric gene in the designated chromosome 13 that encodes a transcriptional regulatory protein in 75% of cases. (1) Another variant t(1;13)(q36;q14) translocation fuses the 5' portion of the PAX7 gene on chromosome 1 with the FOXO1 gene on chromosome 13 in a smaller number of cases (10%). The PAX3-FOXO1 fusion is associated with a worse prognosis than the PAX7-FOXO1 fusion.

Useful For: Supporting the diagnosis of alveolar rhabdomyosarcoma

Interpretation: A positive PAX3-FOXO1 or PAX7-FOXO1 result is consistent with a diagnosis of alveolar rhabdomyosarcoma (ARMS). Sarcomas other than ARMS, and carcinomas, melanomas, and lymphomas are negative for the fusion products. A negative result does not rule out a diagnosis of ARMS.

Reference Values:
An interpretative report will be provided.


Clinical Information: Alveolar soft-part sarcoma (ASPS)/Renal Cell Carcinoma (RCC), Xp11.23 (TFE3), FISH, Tissue

ASPS is a rare malignant tumor typically occurring in patients in their 20s to 30s within the muscle and deep tissues of the extremities. ASPS is slow growing and refractory to chemotherapy with a propensity to metastasize. Prolonged survival is possible even with metastasis, although the long-term disease-related mortality rate is high. ASPS is characterized by a translocation that results in fusion of TFE3 on chromosome Xp11.2 with ASPSCR1 (also called ASPL or RCC17) on chromosome 17q25.3. Both balanced and unbalanced forms (loss of the derivative X chromosome) of the translocation have been observed. Another tumor, a rare subset of papillary renal cell carcinoma (RCC) with a distinctive pathologic morphology, has rearrangements of TFE3 with ASPSCR1 or other fusion partner genes. This tumor predominantly affects children and young adults, presents at an advanced stage but with an indolent clinical course, and is a distinct entity in the World Health Organization classification. Typically a balanced form of the translocation is present in the RCC variant. An assay to detect rearrangement of TFE3 is useful to resolve diagnostic uncertainty in these tumor types, as immunohistochemistry for TFE3 is not reliable.
Useful For: An aid in the diagnosis of alveolar soft-part sarcoma or renal cell carcinoma variant when used in conjunction with an anatomic pathology consultation

Interpretation: A neoplastic clone is detected when the percent of nuclei with the abnormality exceeds the established normal cutoff for the TFE3 probe set. A positive result of TFE3 rearrangement is consistent with a diagnosis of alveolar soft-part sarcoma (ASPS) or renal cell carcinoma (RCC) variant. A negative result suggests that TFE3 is not rearranged, but does not exclude the diagnosis of ASPS or RCC variant.

Reference Values:
An interpretive report will be provided.


Amantadine (Symmetrel)

Reference Values:
Units: ng/mL

Therapeutic range has not been established.

Expected steady state amantadine concentrations in patients receiving recommended daily dosages:
200-1000 ng/mL
Toxicity reported at greater than 2000 ng/mL

Amikacin, Peak, Serum

Clinical Information: Amikacin is an aminoglycoside used to treat severe blood infections by susceptible strains of gram-negative bacteria. Aminoglycosides induce bacterial death by irreversibly binding bacterial ribosomes to inhibit protein synthesis. Amikacin is minimally absorbed from the gastrointestinal tract, and thus can be used orally to reduce intestinal flora. Peak serum concentrations are seen 30 minutes after intravenous infusion, or 60 minutes after intramuscular administration. Serum half-lives in patients with normal renal function are generally 2 to 3 hours. Excretion of aminoglycosides is principally renal, and all aminoglycosides may accumulate in the kidney at 50 to 100 times the serum concentration. Toxicity can present as dizziness, vertigo, or, if severe, ataxia and a Meniere disease-like syndrome. Auditory toxicity may be manifested by simple tinnitus or any degree of hearing loss, which may be temporary or permanent, and can extend to total irreversible deafness. Nephrotoxicity is most frequently manifested by transient proteinuria or azotemia, which may occasionally be severe. Aminoglycosides also are associated with variable degrees of neuromuscular blockade leading to apnea.

Useful For: Monitoring adequacy of serum concentration during amikacin therapy

Interpretation: For conventional (nonpulse) dosing protocols, clinical effects may not be achieved if the peak serum concentration is <20.0 mcg/mL. Toxicity may occur if the peak serum concentration is maintained >35.0 mcg/mL for a prolonged period of time.

Reference Values:
Peak: 20.0-35.0 mcg/mL Toxic peak: >40.0 mcg/mL

**Amikacin, Random, Serum**

**Clinical Information:** Amikacin is an aminoglycoside used to treat severe blood infections by susceptible strains of gram-negative bacteria. Aminoglycosides induce bacterial death by irreversibly binding bacterial ribosomes to inhibit protein synthesis. Amikacin is minimally absorbed from the gastrointestinal tract, and thus can be used orally to reduce intestinal flora. Peak serum concentrations are seen 30 minutes after intravenous infusion, or 60 minutes after intramuscular administration. Serum half-lives in patients with normal renal function are generally 2 to 3 hours. Excretion of aminoglycosides is principally renal, and all aminoglycosides may accumulate in the kidney at 50 to 100 times the serum concentration. Toxicity can present as dizziness, vertigo, or, if severe, ataxia and a Meniere disease-like syndrome. Auditory toxicity may be manifested by simple tinnitus or any degree of hearing loss, which may be temporary or permanent, and can extend to total irreversible deafness. Nephrotoxicity is most frequently manifested by transient proteinuria or azotemia, which may occasionally be severe. Aminoglycosides also are associated with variable degrees of neuromuscular blockade leading to apnea.

**Useful For:** Monitoring adequacy of blood concentration during amikacin therapy

**Interpretation:** For conventional (nonpulse) dosing protocols, clinical effects may not be achieved if the peak serum concentration is <20.0 mcg/mL. Toxicity may occur if, for prolonged periods of time, peak serum concentrations are maintained >35.0 mcg/mL, or trough concentrations are maintained at >10.0 mcg/mL.

**Reference Values:**
- Peak: 20.0-35.0 mcg/mL
- Toxic peak: >40.0 mcg/mL
- Trough: <8.0 mcg/mL
- Toxic trough: >10.0 mcg/mL

**Clinical References:**

**Amikacin, Trough, Serum**

**Clinical Information:** Amikacin is an aminoglycoside used to treat severe blood infections by susceptible strains of gram-negative bacteria. Aminoglycosides induce bacterial death by irreversibly binding bacterial ribosomes to inhibit protein synthesis. Amikacin is minimally absorbed from the gastrointestinal tract, and thus can be used orally to reduce intestinal flora. Peak serum concentrations are seen 30 minutes after intravenous infusion, or 60 minutes after intramuscular administration. Serum half-lives in patients with normal renal function are 2 to 3 hours. Excretion of aminoglycosides is principally renal, and all aminoglycosides may accumulate in the kidney at 50 to 100 times the serum concentration. Toxicity can present as dizziness, vertigo, or, if severe, ataxia and a Meniere disease-like syndrome. Auditory toxicity may be manifested by simple tinnitus or any degree of hearing loss, which may be temporary or permanent, and can extend to total irreversible deafness. Nephrotoxicity is most frequently manifested by transient proteinuria or azotemia, which may occasionally be severe. Aminoglycosides also are associated with variable degrees of neuromuscular blockade leading to apnea.

**Useful For:** Monitoring adequate clearance of amikacin near the end of a dosing cycle

**Interpretation:** For conventional (nonpulse) dosing protocols, trough concentrations should fall to <8.0 mcg/mL. Toxicity may occur if the trough serum concentration is maintained >10.0 mcg/mL for prolonged periods of time.

**Reference Values:**

**Clinical Information:** Maple syrup urine disease (MSUD) is an inborn error of metabolism caused by the deficiency of the branched-chain ketoacid dehydrogenase (BCKDH) complex. The BCKDH complex is involved in the metabolism of the branched-chain amino acids (BCAA): isoleucine (Ile), leucine (Leu), and valine (Val). MSUD patients can be divided into 5 phenotypes: classic, intermediate, intermittent, thiamine-responsive, and dihydrolipoyl dehydrogenase (E3)-deficient depending on the clinical presentation and response to thiamine administration. Classic MSUD which is the most common and most severe form, presents in the neonate with feeding intolerance, failure to thrive, vomiting, lethargy, and maple syrup odor to urine and cerumen. If untreated, it progresses to irreversible mental retardation, hyperactivity, failure to thrive, seizures, coma, cerebral edema, and possibly death. Age of onset for individuals with variant forms of MSUD is variable and some have initial symptoms as early as 2 years of age. Symptoms include poor growth and feeding, irritability, and developmental delays. These patients can also experience severe metabolic intoxication and encephalopathy during periods of sufficient catabolic stress. MSUD is a panethnic condition, but is most prevalent in the Old Order Mennonite community in Lancaster, Pennsylvania with an incidence there of 1:760 live births. The incidence of MSUD is approximately 1:185,000 live births in the general population. Treatment of MSUD aims to normalize the concentration of BCAA by dietary restriction of these amino acids. Because BCAA belong to the essential amino acids, the dietary treatment requires frequent adjustment, which is accomplished by regular determination of BCAA and allo-isoleucine concentrations. Orthotopic liver transplantation has been used with success and is an effective therapy for MSUD.

**Useful For:** Follow-up of patients with maple syrup urine disease Monitoring of dietary compliance for patients with maple syrup urine disease

**Interpretation:** The quantitative results of isoleucine, leucine, valine, and allo-isoleucine with age-dependent reference values are reported without added interpretation. When applicable, reports of abnormal results may contain an interpretation based on available clinical interpretation.

**Reference Values:**

**ISOLEUCINE**
- < or =23 months: 31-105 nmol/mL
- 2-17 years: 30-111 nmol/mL
- > or =18 years: 36-107 nmol/mL

**LEUCINE**
- < or =23 months: 48-175 nmol/mL
- 2-17 years: 51-196 nmol/mL
- > or =18 years: 68-183 nmol/mL

**VALINE**
- < or =23 months: 83-300 nmol/mL
- 2-17 years: 106-320 nmol/mL
- > or =18 years: 136-309 nmol/mL

**ALLO-ISOLEUCINE**
- < or =23 months: <2 nmol/mL
- 2-17 years: <3 nmol/mL
- > or =18 years: <5 nmol/mL

**Clinical References:** 1. Scriver's The Online Metabolic and Molecular Bases of Inherited Disease
Amino Acids, Quantitative, Plasma

Clinical Information: Amino acids are the basic structural units that comprise proteins and are found throughout the body. Many inborn errors of amino acid metabolism, including phenylketonuria and tyrosinemia, have been identified. Amino acid disorders can manifest at any age, but most become evident in infancy or early childhood. These disorders result in the accumulation or the deficiency of 1 or more amino acids in biological fluids, which leads to the clinical signs and symptoms of the particular amino acid disorder. The clinical presentation is dependent upon the specific amino acid disorder. In general, affected patients may experience failure to thrive, neurologic symptoms, digestive problems, dermatologic findings, and physical and cognitive delays. If not diagnosed and treated promptly, amino acid disorders can result in mental retardation and death. Treatment for amino acid disorders includes very specific dietary modifications. Nonessential amino acids are synthesized by the body, while essential amino acids are not and must be obtained through an individual's diet. Therapeutic diets are coordinated and closely monitored by a dietician and/or physician. They are structured to provide the necessary balance of amino acids with particular attention to essential amino acids and those that accumulate in a particular disorder. Patients must pay close attention to the protein content in their diet and generally need to supplement with medical formulas and foods. Dietary compliance is monitored by periodic analysis of plasma amino acids. In addition, plasma amino acid analysis may have clinical importance in the evaluation of several acquired conditions including endocrine disorders, liver diseases, muscle diseases, neoplastic diseases, neurological disorders, nutritional disturbances, renal failure, and burns.

Useful For: Evaluation of patients with possible inborn errors of metabolism May aid in evaluation of endocrine disorders, liver diseases, muscle diseases, neoplastic diseases, neurological disorders, nutritional disturbances, renal failure, and burns

Interpretation: When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies at Mayo Clinic or elsewhere, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:

Plasma Amino Acid Reference Values (nmol/mL) Age Groups

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>(n=191) 2-17 Years (n=441)</th>
<th>&gt; or =18 Years (n=148)</th>
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<tr>
<td>Phosphoethanolamine (PEtN)</td>
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<td>Histidine (His)</td>
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<td>Threonine (Thr)</td>
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**Amino Acids, Quantitative, Random, Urine**

**Clinical Information:** Amino acids are the basic structural units that comprise proteins and are found throughout the body. Many inborn errors of amino acid metabolism that affect amino acid transport or metabolism have been identified, such as phenylketonuria and tyrosinemia. Amino acid disorders can manifest at any age, but most become evident in infancy or early childhood. These disorders result in the accumulation or the deficiency of 1 or more amino acids in biological fluids, which leads to the clinical signs and symptoms of the particular amino acid disorder. The clinical presentation is dependent upon the specific amino acid disorder. In general, affected patients may experience failure to thrive, neurologic symptoms, digestive problems, dermatologic findings, and physical and cognitive delays. If not diagnosed and treated promptly, amino acid disorders can result in mental retardation and death. In addition, amino acid analysis may have clinical importance in the evaluation of several acquired conditions including endocrine disorders, liver diseases, muscle diseases, neoplastic diseases, neurological disorders, nutritional disturbances, renal failure, and burns. General elevations in urine amino acid levels, called aminoaciduria, can be seen in disorders with amino acid transport defects such as lysinuric protein intolerance and Hartnup disease, as well as in conditions with renal tubular dysfunction including Lowe syndrome and Dent disease.

**Useful For:** Evaluating patients with possible inborn errors of metabolism May aid in evaluation of endocrine disorders, liver diseases, muscle diseases, neoplastic diseases, neurological disorders, nutritional disturbances, renal failure, and burns

**Interpretation:** When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and in vitro confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies at Mayo or elsewhere, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

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metabolism have been identified. Amino acid disorders can manifest at any age, but most become evident in infancy or early childhood. These disorders result in the accumulation or deficiency of 1 or more amino acids in biological fluids, which leads to the clinical signs and symptoms of the particular amino acid disorder. The clinical presentation is dependent upon the specific amino acid disorder. In general, affected patients may experience failure to thrive, neurologic symptoms, digestive problems, dermatologic findings, and physical and cognitive delays. If not diagnosed and treated promptly, amino acid disorders can result in mental retardation and death. Cerebrospinal fluid (CSF) specimens are highly informative for a subset of these conditions, such as nonketotic hyperglycinemia and serine biosynthesis defects. CSF specimens are most informative when a plasma specimen is drawn at the same time and the ratio of the amino acid concentrations in CSF to plasma is calculated.

**Useful For:** Evaluating patients with possible inborn errors of amino acid metabolism, in particular nonketotic hyperglycinemia and serine biosynthesis defects, especially when used in conjunction with concomitantly drawn plasma specimens.

**Interpretation:** When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is provided. This interpretation includes an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional biochemical testing and in vitro confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies at Mayo Clinic or elsewhere, and the telephone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

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<th>CSF Amino Acid Reference Values</th>
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<th>Reference Values (nmol/mL)</th>
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Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
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<td>Gamma-amino-n-butyric Acid (GABA)</td>
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**AAUCD 60202**

**Amino Acids, Urea Cycle Disorders Panel, Plasma**

**Clinical Information:** Urea cycle disorders (UCD) are a group of inherited disorders of nitrogen detoxification that result when any of the enzymes in the urea cycle (carbamoylphosphate synthetase I: CPS I; ornithine transcarbamylase: OTC; argininosuccinic acid synthetase; argininosuccinic acid lyase; arginase; or the cofactor producer, N-acetyl glutamate synthetase: NAGS), have deficient or reduced activity. The urea cycle serves to break down nitrogen, and defects in any of the steps of the pathway can result in an accumulation of ammonia, which can be toxic to the nervous system. Infants with a complete enzyme deficiency typically appear normal at birth, but present in the neonatal period as ammonia levels rise with lethargy, seizures, hyper- or hypoventilation, and ultimately coma or death. Individuals with partial enzyme deficiency may present later in life, typically following an acute illness or other stressor. Symptoms may be less severe and may present with episodes of psychosis, lethargy, cyclical vomiting, and behavioral abnormalities. All of the UCDs are inherited as autosomal recessive disorders, with the exception of OTC deficiency, which is X-linked. UCDs may be suspected with elevated ammonia, normal
anion gap, and a normal glucose. Plasma amino acids can be used to aid in the diagnosis of a UCD. Measurement of urinary orotic acid, enzyme activity (CPS I, OTC, or NAGS), and molecular genetic testing can help to distinguish the conditions and allows for diagnostic confirmation. Acute treatment for UCDs consists of dialysis and administration of nitrogen scavenger drugs to reduce ammonia concentration. Chronic management typically involves restriction of dietary protein with essential amino acid supplementation. More recently, orthotopic liver transplantation has been used with success in treating some patients.

**Useful For:** Differential diagnosis and follow-up of patients with urea cycle disorders

**Interpretation:** The quantitative results of glutamine, ornithine, citrulline, arginine, and argininosuccinic acid with age-dependent reference values are reported without added interpretation. When applicable, reports of abnormal results may contain an interpretation based on available clinical interpretation.

**Reference Values:**

**GLUTAMINE**
- < or =23 months: 316-1020 nmol/mL
- 2-17 years: 329-976 nmol/mL
- > or =18 years: 371-957 nmol/mL

**ORNITHINE**
- < or =23 months: 20-130 nmol/mL
- 2-17 years: 22-97 nmol/mL
- > or =18 years: 38-130 nmol/mL

**CITRULLINE**
- < or =23 months: 9-38 nmol/mL
- 2-17 years: 11-45 nmol/mL
- > or =18 years: 17-46 nmol/mL

**ARGININE**
- < or =23 months: 29-134 nmol/mL
- 2-17 years: 31-132 nmol/mL
- > or =18 years: 32-120 nmol/mL

**ARGININOSUCCINIC ACID**
- <2 nmol/mL
  - Reference value applies to all ages.

**Clinical References:**

**Aminolevulinic Acid (ALA), Urine**

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. See The Heme Biosynthetic Pathway in Special Instruction for more information. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrias can be further
classified as chronic or acute, based on their clinical presentation. The primary acute hepatic porphyrias: aminolevulinic acid dehydratase deficiency porphyria (ADP), acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms that typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. A broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes may precipitate crises. Photosensitivity is not associated with AIP, but may be present in HCP and VP. The excretion of aminolevulinic acid (ALA) can be increased due to one of the inherited acute porphyrias or due to secondary inhibition of ALA dehydratase. Among the secondary causes, acute lead intoxication results in the greatest increases of aminolevulinic aciduria. Less significant elevations are seen in chronic lead intoxication, tyrosinemia type I, alcoholism, and pregnancy. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies.

**Useful For:** Assistance in the differential diagnosis of the various acute hepatic porphyrias

**Interpretation:** Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

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<th>Female Ref Interval</th>
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<tbody>
<tr>
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</tr>
<tr>
<td>1-17 years</td>
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</tr>
<tr>
<td>&gt; or =18 years</td>
<td>&lt; or =15 nmol/mL</td>
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**Clinical References:**

### Aminolevulinic Acid (ALA), Urine

**Reference Values:**

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<tr>
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<td>600-2000</td>
<td>400-1300</td>
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<tr>
<td>Aminolevulinic Acid umol/L</td>
<td>umol/L</td>
<td>0-35</td>
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</table>

Current as of October 11, 2018 2:20 pm CDT   800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Aminolevulinic Acid Dehydratase (ALAD), Washed Erythrocytes

**Clinical Information:** Porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. A defect in the second enzyme of this pathway causes 5-aminolevulinic acid (ALA) dehydratase (ALAD) deficiency porphyria (ADP). A marked deficiency of ALAD causes the accumulation and subsequent urinary excretion of large amounts of ALA. Urinary porphobilinogen (PBG) remains essentially normal, which rules out other forms of acute porphyria. ADP is an autosomal recessive acute hepatic porphyria that produces neurologic symptoms similar to those seen in acute intermittent porphyria. Symptoms include acute abdominal pain, peripheral neuropathy, nausea, vomiting, constipation, and diarrhea. Respiratory impairment, seizures, and psychosis are possible during an acute period. ADP is extremely rare with only 7 cases described in the literature since 1979. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies.

**Useful For:** Confirmation of a diagnosis of aminolevulinic acid dehydratase deficiency porphyria

**Interpretation:** Abnormal results are reported with a detailed interpretation including an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available, and a phone number to reach a laboratory director in case the referring physician has additional questions.

**Reference Values:**
Reference ranges have not been established for patients who are <16 years of age.

- \( > 4.0 \text{ nmol/L/sec} \)
- \( 3.5-3.9 \text{ nmol/L/sec} \) (indeterminate)
- \( < 3.5 \text{ nmol/L/sec} \) (diminished)

**Clinical References:**

Aminolevulinic Acid Dehydratase (ALAD), Whole Blood

**Clinical Information:** Porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. A defect in the second enzyme of this pathway causes 5-aminolevulinic acid (ALA) dehydratase (ALAD) deficiency porphyria (ADP). A marked deficiency of ALAD causes the accumulation and subsequent urinary excretion of large amounts of ALA. Urinary porphobilinogen (PBG) remains essentially normal, which rules out other forms of acute porphyria. ADP is an autosomal recessive acute hepatic porphyria that produces neurologic symptoms similar to those seen in acute intermittent porphyria. Symptoms include acute abdominal pain, peripheral neuropathy, nausea, vomiting, constipation, and diarrhea. Respiratory impairment, seizures, and psychosis are possible during an acute period. ADP is extremely rare with only 7 cases described in the
literature since 1979. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies.

**Useful For:** This test is the preferred test for the confirmation of a diagnosis of aminolevulinic acid dehydratase deficiency porphyria

**Interpretation:** Abnormal results are reported with a detailed interpretation including an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available, and a phone number to reach a laboratory director in case the referring physician has additional questions.

**Reference Values:**
Reference ranges have not been established for patients who are <16 years of age.

- > or =4.0 nmol/L/sec
- 3.5-3.9 nmol/L/sec (indeterminate)
- <3.5 nmol/L/sec (diminished)

**Clinical References:**

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**Amiodarone, Serum**

**Clinical Information:** Amiodarone is an antiarrhythmic agent used to treat life-threatening arrhythmias; it is typically categorized as a Class III drug (antiarrhythmic agents that are potassium channel blockers) but shows several mechanisms of action. The U.S. Food and Drug Administration approved the use of amiodarone for recurrent ventricular fibrillation and recurrent, hemodynamically unstable ventricular tachycardia only after demonstrating lack of response to other antiarrhythmics, but more recent studies have shown amiodarone to be the antiarrhythmic agent of choice for many situations, including atrial fibrillation.(1) Amiodarone can be administered orally or intravenously for cardiac rhythm control. It is 95% protein bound in blood, with a volume of distribution of 60 L/kg. Amiodarone elimination is quite prolonged, with a mean half-life of 53 days. CYP3A4 converts amiodarone to its equally active metabolite, N-desethylamiodarone (DEA), which displays very similar pharmacokinetics and serum concentrations, compared to the parent drug. (2) Current therapeutic ranges are based solely on amiodarone, but most individuals will have roughly equivalent concentrations of DEA at steady state.(3) Numerous side effects have been associated with amiodarone. The most common adverse effect is disruption of thyroid function (hypo- or hyperthyroidism) due to amiodarone’s structural similarity to thyroid hormones. Neurological and gastrointestinal toxicities are concentration-dependent, whereas thyroid dysfunction, pulmonary fibrosis, and hepatotoxicity are more loosely linked to drug concentration. There is significant potential for drug interactions involving amiodarone, including several other cardiovascular drugs (eg, digoxin, verapamil, class I antiarrhythmics [sodium channel blockers]), warfarin, statins, and CYP3A4 substrates.

**Useful For:** Monitoring amiodarone therapy, especially when amiodarone is coadministered with other drugs that may interact Evaluation of possible amiodarone toxicity Assessment of patient compliance

**Interpretation:** Clinical effects generally require serum concentrations above 0.5 mcg/mL. Increased risk of toxicity is associated with amiodarone concentrations above 2.5 mcg/mL. Although therapeutic and toxic ranges are based only on the parent drug, the active metabolite N-desethylamiodarone should be
present in similar concentrations to amiodarone.

**Reference Values:**

**AMIODARONE**
- Therapeutic concentration: 0.5-2.0 mcg/mL
- Toxic concentration: >2.5 mcg/mL

**DESETHYLAMIODARONE**
- No therapeutic range established; activity and serum concentration are similar to parent drug.

**Clinical References:**

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**AMTRP 63506**

**Amitriptyline and Nortriptyline, Serum**

**Clinical Information:** Amitriptyline is a tricyclic antidepressant that is metabolized to nortriptyline, which has similar pharmacologic activity. The relative blood levels of amitriptyline and nortriptyline are highly variable among patients. Amitriptyline is the drug of choice in treatment of depression when the side effect of mild sedation is desirable. Nortriptyline is used when its stimulatory side effect is considered to be of clinical advantage. Nortriptyline is unique among the antidepressants in that its blood level exhibits the classical therapeutic window effect; blood concentrations above or below the therapeutic window correlate with poor clinical response. Thus, therapeutic monitoring to ensure that the blood level is within the therapeutic window is critical to accomplish successful treatment with this drug. Amitriptyline displays major cardiac toxicity when the combined serum level of amitriptyline and nortriptyline is above 500 ng/mL, characterized by QRS widening, which leads to ventricular tachycardia and asystole. In some patients, toxicity may manifest at lower concentrations. Like amitriptyline, nortriptyline can cause major cardiac toxicity when the concentration is above 500 ng/mL, characterized by QRS widening, which leads to ventricular tachycardia and asystole. In some patients, toxicity may manifest at lower concentrations.

**Useful For:**
- Monitoring serum concentration during therapy
- Evaluating potential toxicity
- The test may also be useful to evaluate patient compliance

**Interpretation:**
- Most individuals display optimal response to amitriptyline when combined serum levels of amitriptyline and nortriptyline are between 80 and 200 ng/mL. Risk of toxicity is increased with combined levels are above 500 ng/mL. Most individuals display optimal response to nortriptyline with serum levels between 70 and 170 ng/mL. Risk of toxicity is increased with nortriptyline levels above 500 ng/mL. Some individuals may respond well outside of these ranges, or may display toxicity within the therapeutic range, thus, interpretation should include clinical evaluation. Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next dose).

**Reference Values:**

**AMITRIPTYLINE AND NORTRIPTYLINE**
- Total therapeutic concentration: 80-200 ng/mL

**NORTRIPTYLINE ONLY**
- Therapeutic concentration: 70-170 ng/mL
- Note: Therapeutic ranges are for specimens drawn at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.

**Clinical References:**
**Ammonia, Plasma**

**Clinical Information:** Ammonia is a waste product of protein catabolism; it is potentially toxic to the central nervous system. Increased plasma ammonia may be indicative of hepatic encephalopathy, hepatic coma in terminal stages of liver cirrhosis, hepatic failure, acute and subacute liver necrosis, and Reye's syndrome. Hyperammonemia may also be found with increasing dietary protein intake. The major cause of hyperammonemia in infants includes inherited deficiencies of urea cycle enzymes, inherited metabolic disorders of organic acids and the dibasic amino acids lysine and ornithine, and severe liver disease.

**Useful For:** Assisting in the diagnosis of hepatic coma Investigating and monitoring treatment for inborn errors of metabolism Evaluating patients with advanced liver disease

**Interpretation:** Plasma ammonia concentrations do not correlate well with the degree of hepatic encephalopathy. Elevated ammonia concentration may also be found with increased dietary protein intake.

**Reference Values:**

< or =30 mcmol/L


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**Ammonium, 24 Hour, Urine**

**Clinical Information:** The kidney regulates acid excretion and systemic acid base balance. Changing the amount of ammonium in the urine is one important way the kidneys accomplish this task. Thus, measuring the urine ammonium level can provide understanding of the cause of an acid base disturbance in individual patients.(1-3) The urine ammonium level can also provide a lot of information about the daily acid production in a given patient. Since most of an individual's acid load comes from ingested protein, the urine ammonium is a good indicator of dietary protein intake. Urine ammonium measurements can be particularly helpful for the diagnosis and treatment of kidney stone patients: -High urine ammonium and low urinary pH suggests ongoing gastrointestinal losses. Such patients are at risk of uric acid and calcium oxalate stones. -Low urine ammonium and high urine pH suggests renal tubular acidosis. Such patients are at risk of calcium phosphate stones. -Patients with calcium oxalate and calcium phosphate stones are often treated with citrate to raise the urine citrate (a natural inhibitor of calcium oxalate and calcium phosphate crystal growth). However, since citrate is metabolized to bicarbonate (a base), this drug can also increase the urine pH. If the urine pH gets too high with citrate treatment, one may unintentionally increase the risk of calcium phosphate stones. Monitoring the urine ammonium is one way to titrate the citrate dose and avoid this problem. A good starting citrate dose is about one-half of the urine ammonium excretion (in mEq of each). One can monitor the effect of this dose on urine ammonium, citrate, and pH values, and adjust the citrate dose based upon the response. A fall in urine ammonium should indicate whether the current citrate is enough to partially (but not completely) counteract the daily acid load of that given patient.(4)

**Useful For:** Diagnosis of the cause of an acidosis Diagnosis and treatment of kidney stones

**Interpretation:** If a patient has an acidosis, and the amount of ammonium in the urine is low, this suggests a renal tubular acidosis. If the amount of ammonium is high, this suggests that the kidneys are working normally and that there are other losses of bicarbonate in the body. Typically this implies gastrointestinal losses.

**Reference Values:**

15-56 mmol/24 hour

Reference values have not been established for patients <18 years and >77 years of age.
Reference values apply to 24 hour collections.

**Clinical References:**

### RAMCN
**36885**
**Ammonium, Random, Urine**

**Reference Values:**
Only orderable as part of a profile. For more information see SSATR / Supersaturation Profile, Pediatric, Random, Urine.

### RAMBO
**62657**
**Ammonium, Random, Urine**

**Clinical Information:**
The kidney regulates acid excretion and systemic acid base balance. Changing the amount of ammonium in the urine is one important way the kidneys accomplish this task. Thus, measuring the urine ammonium level can provide understanding of the cause of an acid base disturbance in individual patients.(1-3) The urine ammonium level can also provide a lot of information about the daily acid production in a given patient. Since most of an individual's acid load comes from ingested protein, the urine ammonium is a good indicator of dietary protein intake. Urine ammonium measurements can be particularly helpful for the diagnosis and treatment of kidney stone patients: -High urine ammonium and low urinary pH suggests ongoing gastrointestinal losses. Such patients are at risk of uric acid and calcium oxalate stones. -Low urine ammonium and high urine pH suggests renal tubular acidosis. Such patients are at risk of calcium phosphate stones. -Patients with calcium oxalate and calcium phosphate stones are often treated with citrate to raise the urine citrate (a natural inhibitor of calcium oxalate and calcium phosphate crystal growth). However, since citrate is metabolized to bicarbonate (a base) this drug can also increase the urine pH. If the urine pH gets too high with citrate treatment, one may unintentionally increase the risk of calcium phosphate stones. Monitoring the urine ammonium is one way to titrate the citrate dose and avoid this problem. A good starting citrate dose is about one-half of the urine ammonium excretion (in mEq of each). One can monitor the effect of this dose on urine ammonium, citrate, and pH values, and adjust the citrate dose based upon the response. A fall in urine ammonium should indicate whether the current citrate is enough to partially (but not completely) counteract the daily acid load of that given patient.(4)

**Useful For:**
- Diagnosis of the cause of an acidosis
- Diagnosis and treatment of kidney stones

**Interpretation:**
If a patient has an acidosis, and the amount of ammonium in the urine is low, this suggests a renal tubular acidosis. If the amount of ammonium is high, this suggests that the kidneys are working normally and that there are other losses of bicarbonate in the body. Typically this implies gastrointestinal losses.

**Reference Values:**
Random: 3-65 mmol/L
No reference values established for <18 years and >77 years of age.

**Clinical References:**
**Amniotic Fluid Culture for Genetic Testing**

**Clinical Information:** Fetal cells obtained by amniocentesis (amniocytes) are used for a wide range of laboratory tests. Prior to testing, the cells may need to be cultured to obtain adequate numbers of amniocytes.

**Useful For:** Producing amniocyte cultures that can be used for genetic analysis. Once confluent flasks are established, the amniocyte cultures are sent to other laboratories, either within Mayo Clinic or to external sites, based on the specific testing requested.

**Reference Values:**
Not applicable


**Amobarbital, Serum**

**Clinical Information:** Amobarbital is an intermediate-acting barbiturate with hypnotic properties used in short-term treatment of insomnia and to reduce anxiety and provide sedation preoperatively.(1,2) Amobarbital is administered by intravenous infusion or intramuscular injection. The duration of its hypnotic effect is about 6 to 8 hours. The drug distributes throughout the body, with a volume of distribution of 0.9 to 1.4 L/kg, and about 59% of a dose is bound to plasma proteins. Metabolism takes place in the liver primarily via hepatic microsomal enzymes. Its half-life is about 15 to 40 hours (mean: 25 hours). Excretion occurs mainly in the urine.(2,3)

**Useful For:** Monitoring amobarbital therapy

**Interpretation:** Amobarbital concentrations above 10 mcg/mL have been associated with toxicity.

**Reference Values:**
- Therapeutic concentration: 1.0-5.0 mcg/mL
- Toxic concentration: >10.0 mcg/mL

**Clinical References:**

**Amoxapine (Asendin) and 8-Hydroxyamoxapine**

**Reference Values:**
- Amoxapine: No reference range provided
- 8-Hydroxyamoxapine: No reference range provided
- Combined Total: 200–400 ng/mL

**Amoxicillin, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of
sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>Class</th>
<th>IgE kU/L</th>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
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</tr>
</tbody>
</table>

Reference values apply to all ages.


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**FAMP 91171**

**Amphetamine, Serum or Plasma**

**Reference Values:**

Reference Range: 10 – 100 ng/mL

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**AMPMX 62712**

**Amphetamine-Type Stimulants Confirmation, Chain of Custody, Meconium**

**Clinical Information:** Several stimulants and hallucinogens chemically related to phenylethylamine are referred to collectively as the amphetamine-type stimulants (amphetamines). Generally, this refers to the prescription and illicit amphetamines including amphetamine; methamphetamine; 3,4-methylenedioxyamphetamine (MDMA, Ecstasy); 3,4-methylenedioxyamphetamine (MDA); and 3,4-methylenedioxyethylamphetamine (MDEA).(1) Methamphetamine has become a drug of choice among stimulant abusers because of its availability and ease to synthesize. The metabolism of amphetamine consists of hydroxylation and deamination followed by conjugation with glucuronic acid. Methamphetamine is metabolized to amphetamine; both should be present in urine after methamphetamine use. Both MDMA and MDEA are metabolized to MDA.(1) The disposition of drug in meconium, the first fecal material passed by the neonate, is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing of amniotic fluid.(2) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th
week of gestation, and slowly moves to the colon by the 16th week of gestation.(3) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure up to 5 months before birth, a longer historical measure than is possible by urinalysis.(2) Intrauterine drug exposure to amphetamines has been associated with maternal abruption, prematurity, and decreased growth parameters such as low-birth weight.(4) Some intrauterine amphetamine-exposed infants may develop hypertonia, tremors, and poor feeding and abnormal sleep patterns.(5) Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection of in utero drug exposure up to 5 months before birth

Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

**Interpretation:** The presence of any 1 of the following: amphetamine; methamphetamine; 3,4-methylenedioxymethamphetamine; 3,4-methylenedioxyamphetamine; or 3,4-methylenedioxyethylamphetamine at >50 ng/g is indicative of in utero exposure up to 5 months before birth.

**Reference Values:**

**Negative**

Positives are reported with a quantitative LC-MS/MS result.

**Cutoff concentrations:**

- Amphetamine by LC-MS/MS: 50 ng/g
- Methamphetamine by LC-MS/MS: 50 ng/g
- 3,4-Methylenedioxymethamphetamine by LC-MS/MS: 50 ng/g
- 3,4-Methylenedioxyethylamphetamine by LC-MS/MS: 50 ng/g
- 3,4-Methylenedioxymethamphetamine by LC-MS/MS: 50 ng/g

**Clinical References:**

exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis. (2) Intrauterine drug exposure to amphetamines has been associated with maternal abruption, prematurity, and decreased growth parameters such as low-birth weight. (4) Some intrauterine amphetamine-exposed infants may develop hypertonia, tremors, and poor feeding and abnormal sleep patterns. (5)

**Useful For:** Detection of in utero exposure to amphetamine-type stimulants up to 5 months before birth

**Interpretation:** The presence of any 1 of the following: amphetamine; methamphetamine; 3,4-methylenedioxyamphetamine; 3,4-methylenedioxymethamphetamine; or 3,4-methylenedioxyethylamphetamine at greater than 50 ng/g is indicative of in utero exposure up to 5 months before birth.

**Reference Values:**

<table>
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<tr>
<td></td>
<td>Positives are reported with a quantitative LC-MS/MS result.</td>
</tr>
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</table>

Cutoff concentrations:

- **AMPHETAMINE BY LC-MS/MS**
  - 50 ng/g

- **METHAMPHETAMINE BY LC-MS/MS**
  - 50 ng/g

- **3,4-METHYLENEDIOXYAMPHETAMINE BY LC-MS/MS**
  - 50 ng/g

- **3,4-METHYLENEDIOXYMETHAMPHETAMINE BY LC-MS/MS**
  - 50 ng/g

- **3,4-METHYLENEDIOXYMETHAMPHETAMINE BY LC-MS/MS**
  - 50 ng/g

**Clinical References:**


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**FASCC Amphetamines Analysis, Serum**

**Reference Values:**

**Reference Range:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>50</td>
</tr>
</tbody>
</table>

| Confirmation Threshold  | 10 mg/mL |

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**AMPHX Amphetamines Confirmation, Chain of Custody, Urine**

**Clinical Information:** Amphetamines are sympathomimetic amines that stimulate the central nervous system activity and, in part, suppress the appetite. Phentermine, amphetamine, and methamphetamine are prescription drugs for weight loss. All of the other amphetamines are Class I
Amphetamines Confirmation, Urine

Clinical Information: Amphetamines are sympathomimetic amines that stimulate the central nervous system activity and, in part, suppress the appetite. Phentermine, amphetamine, and methamphetamine are

Reference Values:

Cutoff concentrations:

- **IMMUNOASSAY SCREEN**
  - <500 ng/mL

- **AMPHETAMINE BY LC-MS/MS**
  - <25 ng/mL

- **METHAMPHETAMINE BY LC-MS/MS**
  - <25 ng/mL

- **PHENTERMINE BY LC-MS/MS**
  - <25 ng/mL

- **METHYLENEDIOXYAMPHETAMINE BY LC-MS/MS**
  - <25 ng/mL

- **METHYLENEDIOXYMETHAMPHETAMINE BY LC-MS/MS**
  - <25 ng/mL

- **PSEUDOEPHEDRINE/EPHEDRINE BY LC-MS/MS**
  - <25 ng/mL reported as negative

prescription drugs for weight loss. All of the other amphetamines are Class I (distribution prohibited) compounds. In addition to their medical use as anorectic drugs, they are used in the treatment of narcolepsy, attention-deficit disorder/attention-deficit hyperactivity disorder and minimal brain dysfunction. Because of their stimulant effects, the drugs are commonly sold illicitly and abused. Physiological symptoms associated with very high amounts of ingested amphetamine or methamphetamine include elevated blood pressure, dilated pupils, hyperthermia, convulsions, and acute amphetamine psychosis.

**Useful For:** Confirming drug exposure involving amphetamines such as amphetamine and methamphetamine, phentermine, methylenedioxymphetamine (MDA), methylenedioxymethamphetamine (MDMA), and methylenedioxyethylamphetamine (MDEA)

**Interpretation:** The presence of amphetamines in urine at concentrations greater than 500 ng/mL is a strong indicator that the patient has used one of these drugs within the past 3 days. Methamphetamine has a half-life of 9 to 24 hours and is metabolized by hepatic demethylation to amphetamine. Consequently, a sample containing methamphetamine usually also contains amphetamine. Amphetamine has a half-life of 4 to 24 hours. Amphetamine is not metabolized to methamphetamine; absence of methamphetamine in the presence of amphetamine indicates the primary drug of abuse is amphetamine. 3,4-Methylenedioxymethamphetamine (Ecstasy, MDMA) is metabolized to 3,4-methylenedioxyamphetamine (MDA). The detection interval in urine for amphetamine type stimulants is typically to 3 to 5 days after last ingestion. This test will produce true-positive results for urine specimens collected from patients who are administered Adderall and Benzedrine (contain amphetamine); Desoxyn and Vicks Inhaler (contain methamphetamine); Selegeline, and famprofazone (metabolized to methamphetamine and amphetamine); and clobenzorex, fenproporex, and mfenorex, which are metabolized to amphetamine.

**Reference Values:**

Negative

Cutoff concentrations:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPHETAMINE BY LC-MS/MS</td>
<td>&lt;25 ng/mL</td>
</tr>
<tr>
<td>METHAMPHETAMINE BY LC-MS/MS</td>
<td>&lt;25 ng/mL</td>
</tr>
<tr>
<td>PHENTERMINE BY LC-MS/MS</td>
<td>&lt;25 ng/mL</td>
</tr>
<tr>
<td>METHYLENEDIOXYAMPHETAMINE BY LC-MS/MS</td>
<td>&lt;25 ng/mL</td>
</tr>
<tr>
<td>METHYLENEDIOXYMETHAMPHETAMINE BY LC-MS/MS</td>
<td>&lt;25 ng/mL</td>
</tr>
<tr>
<td>PSEUDOEPHEDRINE/EPHEDRINE BY LC-MS/MS</td>
<td>&lt;25 ng/mL reported as negative</td>
</tr>
</tbody>
</table>


**Amylase, Body Fluid**

**Clinical Information:** Amylases are a group of hydrolases that degrade complex carbohydrates into fragments. Amylase is produced by the exocrine pancreas and the salivary glands to aid in the digestion of starch. It is also produced by the small intestine mucosa, ovaries, placenta, liver, and fallopian tubes. If ascites are present, amylase is occasionally used to demonstrate pancreatic inflammation. If this is
true, the level will be at least 10 times that of serum.

Useful For: Evaluation of patients suspected of having acute pancreatitis

Interpretation: No control range has been obtained so interpretation is qualitative and thought to be positive for pancreatitis if levels are greater than 1,100 U/L (10 times the serum normal range).

Reference Values:
Not applicable


Amylase, Isoenzymes

Reference Values:
Pancreatic amylase
6-35 months: 2-28 U/L
3-6 years: 8-34 U/L
7-17 years: 9-39 U/L
18 years and older: 12-52 U/L

Salivary amylase
18 months and older: 9-86 U/L

Total amylase
3-90 days: 0-30 U/L
3-6 months: 7-40 U/L
7-8 months: 7-57 U/L
9-11 months: 11-70 U/L
12-17 months: 11-79 U/L
18-35 months: 19-92 U/L
3-4 years: 26-106 U/L
5-12 years: 30-119 U/L
13 years and older: 30-110 U/L

Amylase, Pancreatic Cyst

Clinical Information: Amylases are a group of hydrolases that degrade complex carbohydrates into fragments. Amylase is produced by the exocrine pancreas and the salivary glands to aid in the digestion of starch. It is also produced by the small intestine mucosa, ovaries, placenta, liver, and fallopian tubes. Measurement of amylase in pancreatic cyst fluid is often used in conjunction with tumor markers, carcinoembryonic antigen and CA19-9, as an aid in the differential diagnosis of pancreatic cysts lesions. Amylase seems to be particularly helpful in excluding pancreatic pseudocysts. A number of studies have demonstrated that amylase levels are typically very high, usually in the thousands in pseudocysts, therefore, low amylase values virtually excludes pseudocysts. Based on the evidence available, the American College of Gastroenterology (ACG) practice guidelines for the Diagnosis and Management of Neoplastic Pancreatic Cysts suggest that an amylase cutoff value of 250 U/L is useful to exclude pseudocysts.

Useful For: Aids in distinguishing between pseudocysts and other types of pancreatic cysts, when used in conjunction with imaging studies, cytology, and other pancreatic cyst fluid tumor markers

Interpretation: A pancreatic cyst fluid amylase concentration of <250 U/L indicates a low risk of a pseudocyst and is more consistent with cystic neoplasms such as mucinous cystic neoplasms (MCN), intraductal papillary mucinous neoplasm (IPMN), serous cystadenomas, cystic neuroendocrine tumor, and mucinous cystadenocarcinoma. High pancreatic cyst fluid amylase values are nonspecific and occur both
in pseudocysts and some mucin-producing cystic neoplasms including MCN, IPMN, and mucinous cystadenocarcinoma. In-house studies to verify this cutoff value showed that 94% (66/70) of pseudocysts had a value of > or =250 U/L. Cysts with amylase levels of <250 U/L included 69% of adenocarcinomas, 31% of intraductal papillary mucinous neoplasia, 55% of mucinous cystadenomas, 64% serous cystadenomas, and 6% of pseudocysts. Therefore, using a cutoff of <250 U/L to exclude a pseudocyst has 94% sensitivity and 42% specificity.

Reference Values:
An interpretive report will be provided.

Clinical References:

Amylase, Pancreatic, Serum

Clinical Information: Amylases are a group of hydrolases that degrade complex carbohydrates into fragments. Amylase is produced by the exocrine pancreas and the salivary glands to aid in the digestion of starch. It is also produced by the small intestine mucosa, ovaries, placenta, liver, and fallopian tubes. Since the clinical use of amylase activity is usually to detect pancreatitis, the pancreatic amylase (p-amylase) form provides the single most useful test in the laboratory diagnosis of acute pancreatitis. Total serum amylase continues to be the most widely used clinical test for the diagnosis of acute pancreatitis. Its use has been justified on the basis of its accuracy of 95%. The problem with its use is that it has relatively low specificity of between 70% and 80%.

Useful For: Diagnosing acute pancreatitis

Interpretation: Pancreatic amylase is elevated in acute pancreatitis within 12 hours of onset and persists 3 to 4 days. The elevation is usually 4-fold to 6-fold the upper reference limit. Macroamylase may cause less dramatic and more persistent elevations of p-amylase over weeks or months. This is usually accompanied by a reduced amylase clearance. Values over the normal reference interval in patients with histories consistent with acute pancreatitis are confirmatory. Peak values are often 200 U/L or higher. Macroamylasemia may cause small, but persistent elevations of amylase. An elevation of total serum alpha-amylase does not specifically indicate a pancreatic disorder since the enzyme is produced by the salivary glands, mucosa of the small intestine, ovaries, placenta, liver, and the lining of the fallopian tubes. Two isoenzymes, pancreatic and salivary, are found in serum. Pancreatic amylase has been shown to be more useful than total amylase when evaluating patients with acute pancreatitis.

Reference Values:
0-<24 months: 0-20 U/L  
2-<18 years: 9-35 U/L  
> or =18 years: 11-54 U/L

Clinical References:

Amylase, Random, Urine

Clinical Information: Amylases are enzymes that hydrolyze complex carbohydrates. They are produced by a number of organs and tissues, predominantly the exocrine pancreas (P-type amylase) and salivary glands (S-type amylase). Plasma amylases are of relatively low molecular weight for an enzyme (55,000 to 60,000 daltons) and enter the urine through glomerular filtration. Conditions that cause increased entry of amylase into plasma (eg, acute pancreatitis) will thus result in increased urinary
excretion of amylase. Urinary amylase is therefore sometimes used in the diagnosis of acute pancreatitis. However, the rate of urinary amylase excretion appears to be less sensitive than plasma markers, and is not specific for the diagnosis of acute pancreatitis. Similar to other low molecular weight proteins filtered by glomeruli, amylases are reabsorbed to an extent by the proximal tubule. Thus, conditions associated with increased production and glomerular filtration of other low molecular weight proteins that compete with tubular reabsorption of amylase, or conditions of proximal tubular injury may increase urinary amylase excretion. Also, a number of disorders other than acute pancreatitis may cause increases in plasma amylase concentrations and consequent increases in urinary amylase excretion. These conditions include burns, ketoacidosis, myeloma, light-chain proteinuria, march hemoglobinuria, acute appendicitis, intestinal perforation, and following extracorporeal circulation.

Urinary amylase clearance is increased about 3-fold for 1 to 2 weeks in patients with acute pancreatitis. A value > 550 U/L has been reported as 62% sensitive and 97% specific for acute pancreatitis (3), while a value > 2000 U/L has been reported as 62% sensitive and 97% specific for acute pancreatitis (4). Quantitation of urinary amylase excretion is also useful in monitoring for rejection following pancreas transplantation. The duodenal cuffs of donor pancreases are often surgically anastomosed to the recipient’s bladder at the time of pancreas transplantation, allowing for drainage of exocrine pancreas fluid into the bladder. In pancreatic rejection, urinary amylase excretion decreases. In patients with pancreas transplants that drain into the urinary system, a drop in urinary amylase of more than 25% from that patient’s baseline value can indicate acute rejection (5). In this situation, collecting a timed urine sample and expressing the urinary amylase level as Units excreted/hr might reduce variability and improve test performance (6).

**Useful For:** Assessment of acute rejection of bladder-drained pancreas transplants Diagnoses of acute pancreatitis

**Interpretation:** Decreases in urinary amylase excretion of greater than 30% to 50%, relative to baseline values, may be associated with acute pancreas allograft rejection. Because there is large day-to-day variability in urinary amylase excretion following pancreas transplantation, if a significant decrease is noted, it should be confirmed by a second collection. There is also large inter-individual variability in urinary amylase excretion among pancreas transplant recipients. Acute rejection is usually not established solely by changes in urinary amylase excretion, but by tissue biopsy. Levels are elevated in acute pancreatitis (but with poor sensitivity and specificity).

**Reference Values:**
No established reference values

**Clinical References:**

**Amylase, Timed Collection, Urine**

**Clinical Information:** Amylases are enzymes that hydrolyze complex carbohydrates. They are produced by a number of organs and tissues, predominantly the exocrine pancreas (P-type amylase) and salivary glands (S-type amylase). Plasma amylases are of relatively low molecular weight for an enzyme (55,000-60,000 daltons) and enter the urine through glomerular filtration. Conditions that cause increased entry of amylase into plasma (eg, acute pancreatitis) will thus result in increased urinary excretion of amylase. Therefore, urinary amylase is sometimes used in the diagnosis of acute pancreatitis. However, the rate of urinary amylase excretion appears to be less sensitive than plasma markers, and is not specific for the diagnosis of acute pancreatitis. Similar to other low-molecular-weight proteins filtered by
glomeruli, amylases are reabsorbed to an extent by the proximal tubule. Thus, conditions associated with increased production and glomerular filtration of other low-molecular-weight proteins that compete with tubular reabsorption of amylase or conditions of proximal tubular injury may increase urinary amylase excretion. Also, a number of disorders other than acute pancreatitis may cause increases in plasma amylase concentrations and consequent increases in urinary amylase excretion. These conditions include burns, ketoacidosis, myeloma, light-chain proteinuria, march hemoglobinuria, acute appendicitis, intestinal perforation, and following extracorporeal circulation. Quantitation of urinary amylase excretion is also useful in monitoring for rejection following pancreas transplantation. The duodenal cuffs of donor pancreases are often surgically anastomosed to the recipient’s bladder at the time of pancreas transplantation, allowing for drainage of exocrine pancreas fluid into the bladder. In pancreatic rejection, urinary amylase excretion decreases.

Useful For: Assessment of acute rejection of bladder-drained pancreas transplants As an aid in the diagnosis of acute pancreatitis

Interpretation: Decreases in urinary amylase excretion of greater than 30% to 50%, relative to baseline values, may be associated with acute pancreas allograft rejection. Because there is large day-to-day variability in urinary amylase excretion following pancreas transplantation, if a significant decrease is noted, it should be confirmed by a second collection. There is also large inter-individual variability in urinary amylase excretion among pancreas transplant recipients. Collecting a timed urine specimen and expressing the urinary amylase level as Units excreted/hour might reduce variability and improve test performance. However, acute rejection is usually not established solely by changes in urinary amylase excretion, but by tissue biopsy. Urinary amylase is elevated in acute pancreatitis, but the test has poor sensitivity and specificity.

Reference Values:
3-26 U/hour

serum assays. In quiescent chronic pancreatitis, both serum and urine activities are usually subnormal.
Because it is produced by several organs, amylase is not a specific indicator of pancreatic function.
Elevated levels also may be seen in a number of nonpancreatic disease processes including mumps,
salivary duct obstruction, ectopic pregnancy, and intestinal obstruction/infarction.

**Reference Values:**
- 0-30 days: 0-6 U/L
- 31-182 days: 1-17 U/L
- 183-365 days: 6-44 U/L
- 1-3 years: 8-79 U/L
- 4-17 years: 21-110 U/L
- ≥18 years: 26-102 U/L

**Clinical References:**

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**Amyloid A (Hepatic) Immunostain, Technical Component Only**

**Clinical Information:** Amyloid A (AA), also called serum amyloid A (SAA), is an acute-phase protein. In the liver, AA is expressed on hepatocytes, although expression has been observed in adipocytes. AA can be used with a panel of immunohistochemical markers (beta-catenin, liver fatty acid binding protein, C-reactive protein, and glutamine synthetase) to distinguish hepatic adenoma from focal nodular hyperplasia and non-neoplastic liver. AA, along with C-reactive protein is overexpressed in inflammatory (type 3) hepatic adenoma and is not detectable in normal liver or in other adenoma types.

**Useful For:** Classification of hepatic adenomas

**Interpretation:** The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**Amyloid A (SAA) Immunostain, Technical Component Only**

**Clinical Information:** Immunohistochemical staining for amyloid A (SAA) produces diffuse, extracellular staining in positive tissues and colocalizes with Congo Red apple-green birefringence. SAA-type amyloid is associated with chronic inflammatory conditions, such as tuberculosis and rheumatoid arthritis. Immunohistochemical classification of amyloid has been largely replaced by subtyping using tandem mass spectrometry analysis on formalin-fixed paraffin-embedded specimens, due to its superior sensitivity and specificity.

**Useful For:** Identification and classification of amyloid subtypes in tissue

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be
performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**AMYPI**

Amyloid P (SAP) Immunostain, Technical Component Only

Clinical Information: Amyloid P (SAP) is a serum protein that is generally incorporated into the extracellular deposits of all amyloid types. Immunohistochemical staining for SAP produces diffuse, extracellular staining in positive tissues, and colocalizes with Congo Red apple-green birefringence. All types of amyloid should be positive for SAP. Immunohistochemical classification of amyloid has been largely replaced by subtyping using tandem mass spectrometry analysis on formalin-fixed paraffin-embedded specimens, due to its superior sensitivity and specificity.

Useful For: Identification of amyloid deposits in tissue

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**FABP**

Amyloid Beta-Protein

Reference Values:

Adult Reference Range(s):

20-80 pg/ml

This test was developed and its performance characteristics determined by Inter Science Institute. It has not been cleared or approved by the US Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

**APPI**

Amyloid Precursor Protein (APP) Immunostain, Technical
Component Only

**Clinical Information:** Amyloid precursor protein (APP) is present in Alzheimer disease-associated plaques, large pyramidal cells as well as smaller neurons, astrocytes, and microglia. Histologic features of Alzheimer disease include the presence of abundant neurofibrillary tangles, neurites, neuritic threads, and neuritic (“senile”) plaques. The main component of senile plaque amyloid is a 39- to 42-amino acid segment referred to as beta amyloid, which is derived from APP.

**Useful For:** Aids in the identification of amyloid precursor protein present in Alzheimer disease

**Interpretation:** The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**AMYPIP**

**70356**

**Amyloid Protein Identification, Paraffin, LC-MS/MS**

**Clinical Information:** Amyloidosis is a group of hereditary and acquired diseases that are unified by extracellular tissue deposition of misfolded proteins resulting in end organ damage. Amyloidosis can be a systemic or localized disease. Although many cases of amyloidosis are hereditary, most are acquired as the result of an underlying monoclonal B-cell/plasma cell malignancy, as a phenomenon of aging, or as the result of long-standing chronic inflammation. Specific amyloid-related diseases are therefore associated with specific amyloid proteins. These include kappa or lambda immunoglobulin light chains (AL amyloid), transthyretin (ATTR amyloid), serum amyloid A (SAA amyloid), and other uncommon subtypes. Because treatment of amyloidosis patients differs radically for the different amyloid subtypes, it is critically important to accurately identify the proteins that constitute the amyloid deposits. The basic diagnosis of amyloidosis is typically achieved by Congo red staining of paraffin-embedded tissue biopsy specimens obtained from diverse anatomic sites and demonstrating Congo red-positive, apple-green birefringent, amyloid deposits in the tissues. The next step is to definitively subtype the amyloid deposits. This test fulfills that need. It relies on laser microdissection of Congo red-positive amyloid deposits followed by analysis by liquid chromatography-tandem mass spectrometry to accurately determine the identity of the proteins that constitute the amyloid.

**Useful For:** Definitive identification of amyloid proteins

**Interpretation:** An interpretation will be provided.

Amyloidosis, Transthyretin-Associated Familial, Reflex, Blood

Clinical Information: The systemic amyloidoses are a group of diseases that result from the abnormal deposition of amyloid in various tissues of the body. They have been classified into 3 major types: primary, secondary, and hereditary. The most common form of amyloidosis (AL) is a disease of the bone marrow called primary systemic AL (immunoglobulin light chain). Secondary AL usually occurs in tandem with chronic infectious or inflammatory diseases, such as rheumatoid arthritis, tuberculosis, or osteomyelitis. Familial or hereditary AL is the least common form. Determining the specific type of AL is imperative in order to provide both an accurate prognosis and appropriate therapies. Familial or hereditary transthyretin AL is an autosomal dominant disorder caused by mutations in the transthyretin gene (TTR). The resulting amino acid substitutions lead to a relatively unstable, amyloidogenic transthyretin (TTR) protein. Most individuals begin to exhibit clinical symptoms between the third and seventh decades of life. Affected individuals may present with a variety of symptoms including sensorimotor and autonomic neuropathy, vitreous opacities, cardiomyopathy, nephropathy, and gastrointestinal dysfunction. TTR-associated AL is progressive over a course of 5 to 15 years and usually ends in death from cardiac or renal failure or malnutrition.

Orthotopic liver transplantation is a treatment option for some patients who are diagnosed in early stages of the disease. Mayo Medical Laboratories recommends a testing strategy that includes both protein analysis by mass spectrometry (MS) and TTR gene analysis by DNA sequencing (ATTRZ / TTR Gene, Full Gene Analysis) for patients in whom TTR-associated familial AL is suspected. The structure of TTR protein in plasma is first determined by MS. The presence of a pathogenic variant in the TTR gene leads to conformational changes in the TTR protein. This ultimately disrupts the stability of the mature TTR protein tetramer, leading to increased amounts of pro-amyloidogenic TTR monomers in the plasma of affected individuals. MS is able to identify mass difference between wild type TTR and variant TTR protein. Only the transthyretin (also known as prealbumin) is analyzed for amino acid substitutions. Other proteins involved in other less common forms of familial amyloidosis are not examined. If no alterations are detected, gene analysis will not be performed unless requested by the provider (ie, when the diagnosis is still strongly suspected; to rule out the possibility of a false-negative by MS). In all cases demonstrating a structural change by MS, the entire TTR gene will be analyzed by DNA sequence analysis to identify and characterize the observed alteration (gene mutation or benign polymorphism). More than 90 mutations that cause TTR-associated familial AL have now been identified within the TTR gene. Most of the mutations described to date are single base pair changes that result in an amino acid substitution. Some of these mutations correlate with the clinical presentation of AL. For predictive testing in cases where a familial mutation is known, testing for the specific mutation by DNA sequence analysis (FMTT / Familial Mutation, Targeted Testing) is recommended. These assays do not detect mutations associated with non-TTR forms of familial AL. Therefore, it is important to first test an affected family member to determine if TTR is involved and to document a specific mutation in the family before testing at risk individuals.

Useful For: Diagnosis of adult individuals suspected of having transthyretin-associated familial amyloidosis

Interpretation: The presence of a structural change in transthyretin (TTR) is suggestive of a gene mutation that requires confirmation by DNA sequence analysis. A negative result by mass spectrometry does not rule out a TTR mutation. Mass spectrometric (MS) results are falsely negative if the amino acid substitution does not produce a measurable mass shift for the mutation transthyretin. Approximately 90% of the TTR mutations are positive by MS (see Cautions). After identification of the mutation at the DNA level, predictive testing for at-risk family members can be performed by molecular analysis (FMTT / Familial Mutation, Targeted Testing).

Reference Values:
An interpretive report will be provided.

transthyretin amyloidosis by mass spectrometric peptide mapping and DNA sequence analysis. Anal
Amyloidosis In GeneReviews. Edited by RA Pagon, MP Adam, HH Ardinger, et al: Retrieved February
Skinner M, Costello CE: Detection of transthyretin variants using immunoprecipitation and
matrixassisted laser desorption/ionization bioreactive probes: a clinical application of mass

**ANAID** 45010
**Anaerobe Ident (Bill Only)**
**Reference Values:**
This test is for Billing Purposes Only.
This is not an orderable test.

**ISAN** 45255
**Anaerobe Identification by Sequencing (Bill Only)**
**Reference Values:**
This test is for billing purposes only. This is not an orderable test.

**BATTA** 80931
**Anaerobe Suscep Battery (Bill Only)**
**Reference Values:**
This test is for Billing Purposes Only.
This is not an orderable test.

**ANAP** 81157
**Anaplasma phagocytophilum (Human Granulocytic
Ehrlichiosis) Antibody, Serum**

**Clinical Information:** Human granulocyte ehrlichiosis (HGE) is a zoonotic infection caused by a
rickettsia-like agent. The infection is acquired by contact with Ixodes ticks carrying the HGE agent. The
deer mouse is the animal reservoir and, overall, the epidemiology is very much like that of Lyme disease
and babesiosis. HGE is most prevalent in the upper Midwest and in other areas of the United States that
are endemic for Lyme disease. Since its first description in 1994, there have been approximately 50 cases
of HGE described in the upper Midwest. The cellular target in HGE cases is the neutrophil. The
organisms exist in membrane-lined vacuoles within the cytoplasm of infected host cells. Ehrlichial
inclusions, called morulae, contain variable numbers of organisms. Single organisms, wrapped in vacuolar
membranes have also been observed in the cytoplasm. Ehrlichia species occur in small electron-dense and
large electron-lucent forms, but a clear life cycle has not been elucidated. Diagnosis of human ehrlichiosis
has been difficult because the patient's clinical course is often mild and nonspecific, including fever,
myalgias, arthralgias, and nausea. This is easily confused with other illnesses such as influenza or other
tickborne zoonoses such as Lyme disease, babesiosis, and Rocky Mountain spotted fever. Clues to the
diagnosis of ehrlichiosis in a patient with an acute febrile illness after tick exposure include laboratory
findings of leukopenia or thrombocytopenia and elevated serum aminotransferase levels. However, these
findings may also be present in patients with Lyme disease or babesiosis.

**Useful For:** As an adjunct in the diagnosis of human granulocytic ehrlichiosis

**Interpretation:** A positive result of an immunofluorescence assay (IFA) test (titer ≥ 1:64) suggests
current or previous infection with human granulocytic ehrlichiosis. In general, the higher the titer, the
more likely it is that the patient has an active infection. Seroconversion may also be demonstrated by a
significant increase in IFA titers. During the acute phase of the infection, serologic tests are often
nonreactive, PCR testing is available to aid in the diagnosis of these cases (see EHRL /
Ehrlichia/Anaplasma, Molecular Detection, PCR, Blood).

**Reference Values:**
<1:64
Reference values apply to all ages.


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**Anaplastic Lymphoma Kinase (ALK) Immunostain, Technical Component Only**

**Clinical Information:** A subset of anaplastic large-cell lymphomas show overexpression of anaplastic lymphoma kinase (ALK-1) protein, resulting from a translocation involving the ALK1 gene. The abnormal ALK-1 expression can be in a nuclear and cytoplasmic distribution. Overexpression of ALK-1 protein is also useful in the diagnosis of lung adenocarcinoma and inflammatory myofibroblastic tumor. In normal tissue ALK-1 is negative.

**Useful For:** Identification of ALK overexpression

**Interpretation:** The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**Anatomic Pathology Consultation, Wet Tissue**

**Clinical Information:** Mayo Clinic Rochester is staffed by pathologists whose expertise and special interests cover the entirety of Pathology, from surgical pathology with all of its respective subspecialty areas, to Hematopathology, Renal Pathology, and Dermatopathology. We provide consultation services on difficult diagnostic problems. Consultation cases may be sent by a referring pathologist and directed to one of the pathologists who is an expert in the given area or directed more broadly to the subspecialty group. Cases are frequently shared and sometimes transferred between the pathologists, as deemed appropriate for the type of case/diagnostic problem encountered. Emphasis is placed on prompt and accurate results. Materials received are reviewed in conjunction with the clinical history provided, laboratory findings, radiographic findings (if applicable), and sending pathologist’s report or letter. If additional special stains/studies are needed, the results are included in the final interpretive report. In some cases, electron microscopy and other special procedures are utilized as required. A variety of ancillary studies are available (eg, cytochemistry, immunohistochemistry, immunofluorescence, electron microscopy, mass spectrometry, cytogenetics, and molecular genetics) to aid in establishing a diagnosis. These ancillary studies are often expensive and labor intensive, and are most efficiently utilized and interpreted in the context of the morphologic features. It is our goal to provide the highest possible level of diagnostic consultative service, while trying to balance optimal patient care with a cost-conscious approach to solving difficult diagnostic problems.

**Useful For:** Obtaining a rapid, expert opinion on unprocessed specimens referred by the pathologist

**Interpretation:** Results of the consultation are reported in a formal pathology report which includes
a description of ancillary test results (if applicable) and an interpretive comment. When the case is completed, results may be communicated by a phone call. The formal pathology report is faxed. In our consultative practice, we strive to bring the customer the highest quality of diagnostic pathology, in all areas of expertise, aiming to utilize only those ancillary tests that support the diagnosis in a cost-effective manner, and to provide a rapid turnaround time for diagnostic results.

**ANCH 82345**

**Anchovy, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactoid episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


**AREC 70358**

**Androgen Receptor (AR) Immunostain, Technical Component Only**

**Clinical Information:** Androgen receptor binds testosterone and 5 alpha-dihydrotestosterone and mediates the biologic action of these sex hormones. It is normally expressed in a wide variety of tissues, including the epithelium and stromal cells of the prostate, endometrium, ovary, and breast. Cells of
malignancies and the pituitary gland may also be positive.

**Useful For**: Identification of tumors that express androgen receptor

**Interpretation**: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.


### FANGL 75001

**Androstanediol Glucuronide**

**Reference Values:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepubertal Children</td>
<td>Not Established</td>
</tr>
<tr>
<td>Adult Males</td>
<td>112 â€“ 1046 ng/dL</td>
</tr>
</tbody>
</table>
| Adult Females        | 11 â€“ 249 ng/dL    | Occasionally, normal females with no evidence of hirsutism may have levels well beyond the normal range.

### ANST 9709

**Androstenedione, Serum**

**Clinical Information**: Androstenedione is secreted predominately by the adrenal gland and production is at least partly controlled by adrenocorticotropic hormone (ACTH). It is also produced ACTH-independent in the testes and ovaries from adrenal-secreted dehydroepiandrosterone sulfate (DHEA-S). Androstenedione is a crucial sex-steroid precursor. It lies at the convergence of the 2 biosynthetic pathways that lead from the progestins to the sex-steroids, being derived either via:

- C3-dehydrogenation of dehydroepiandrosterone (DHEA) -Catalyzed by 3-beta-hydroxysteroid dehydrogenase-2 (adrenals and gonads) -17,20-lyase (CYP17A1)-mediated side-chain cleavage of 17-alpha-hydroxyprogesterone (OHPG) Androstenedione production during life mimics the pattern of other androgen precursors. Fetal serum concentrations increase throughout embryonal development and peak near birth at approximately young adult levels. Levels then fall rapidly during the first year of life to low prepubertal values. With the onset of adrenarche, androstenedione rises gradually, a process that accelerates with the onset of puberty, reaching adult levels around age 18. Adrenarche is a poorly understood phenomenon peculiar to higher primates that is characterized by a gradual rise in adrenal androgen production. It precedes puberty, but is not causally linked to it. Early adrenarche is not associated with early puberty, or with any reduction in final height, or overt androgenization, and is generally regarded as a benign condition not requiring intervention. However, girls with early adrenarche may be at increased risk of polycystic ovarian syndrome as adults, and some boys may develop early penile enlargement. Elevated androstenedione levels can cause symptoms or signs of hyperandrogenism in women. Men are usually asymptomatic, but through peripheral conversion of androgens to estrogens can occasionally experience mild symptoms of estrogen excess, such as...
levels. Traditionally, OHPG and urinary pregnanetriol or total ketosteroid excretion are measured to guide increased. The goal of CAH treatment is normalization of cortisol levels and, ideally, also of sex-steroid particularly progesterone, 11-deoxycorticosterone, corticosterone, and 18-hydroxycorticosterone, are estrogens, estradiol), and cortisol are low, while production of mineral corticoid and their precursors, in androgen-precursors (17-alpha-hydroxypregnenolone, OHPG, DHEA-S), androgens (testosterone, cholesterol is elevated. In the also very rare 17-alpha-hydroxylase deficiency, androstenedione, all other STAR (steroidogenic acute regulatory protein) deficiency, all steroid hormone levels are low and (as a consequence of peripheral tissue androstenedione production by 3 beta HSD-1). In the very rare mutation, and cortisol is also low, but OHPG is only mildly, if at all, elevated. Also less common, 3 beta -21-hydroxylase gene (CYP21A2) mutations the most common cause of CAH (>90% of cases), usually have very high levels of androstenedione, often 5- to 10-fold elevations. OHPG levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. In the much less common CYP11A1 mutation, androstenedione levels are elevated to a similar extend as in CYP21A2 mutation, and cortisol is also low, but OHPG is only mildly, if at all, elevated. Also less common, 3 beta HSD-2 deficiency is characterized by low cortisol and substantial elevations in DHEA-S and glucocorticoids. Diagnosis always requires measurement of other androgen precursors (eg, OHPG, 17-alpha-hydroxyprogrenolone, and DHEA-S) and cortisol, in addition to androstenedione. See Steroid Pathways in Special Instructions.

**Useful For:** Diagnosis and differential diagnosis of hyperandrogenism (in conjunction with measurements of other sex-steroids). An initial workup in adults might also include total and bioavailable testosterone (TTBSS / Testosterone, Total and Bioavailable, Serum) measurements. Depending on results, this may be supplemented with measurements of sex hormone-binding globulin (SHBG / Sex Hormone Binding Globulin [SHBG], Serum) and other androgenic steroids (eg, dehydroepiandrosterone sulfate [DHEA-S]). Diagnosis of congenital adrenal hyperplasia (CAH), in conjunction with measurement of other androgenic precursors, particularly, 17-alpha-hydroxyprogesterone (OHPG) (OHPG / 17-Hydroxyprogesterone, Serum), 17 alpha-hydroxyprogrenolone, DHEA-S (DHEA / Dehydroepiandrosterone Sulfate [DHEA-S], Serum), and cortisol (CORT / Cortisol, Serum). Monitoring CAH treatment, in conjunction with testosterone (TTST / Testosterone, Total, Serum), OHPG (OHPG / 17-Hydroxyprogesterone, Serum), DHEA-S (DHEA / Dehydroepiandrosterone Sulfate [DHEA-S], Serum), and DHEA (DHEA / Dehydroepiandrosterone [DHEA], Serum). Diagnosis of premature adrenarche, in conjunction with gonadotropins (FSH / Follicle-Stimulating Hormone [FSH], Serum; LH / Luteinizing Hormone [LH], Serum) and other adrenal and gonadal sex-steroids and their precursors (TTBSS / Testosterone, Total and Bioavailable, Serum or TGRP / Testosterone, Total and Free, Serum; EEST / Estradiol, Serum; DHES / Dehydroepiandrosterone Sulfate [DHEA-S], Serum; DHEA / Dehydroepiandrosterone [DHEA], Serum; SHBG / Sex Hormone Binding Globulin [SHBG], Serum; OHPG / 17-Hydroxyprogesterone, Serum).

**Interpretation:** Elevated androstenedione levels indicate increased adrenal or gonadal androgen production. Mild elevations in adults are usually idiopathic, or related to conditions such as polycystic ovarian syndrome (PCOS) in women, or use of androstenedione supplements in men and women. However, levels greater than or equal to 500 ng/dL can suggest the presence of an androgen-secreting adrenal, or less commonly, a gonadal, tumor. Androstenedione levels are elevated in more than 90% of patients with benign androgen-producing adrenal tumors, usually well above 500 ng/dL. Most androgen-secreting adrenal carcinomas also exhibit elevated androstenedione levels, but more typically show relatively larger elevations in 17-alpha-hydroxyprogesterone (OHPG) and dehydroepiandrosterone sulfate (DHEA-S) than in androstenedione, as they have often lost the ability to produce downstream androgens. Most androgen-secreting gonadal tumors also overproduce androstenedione, but often to lesser degrees than adrenal tumors. They also overproduce testosterone. In men and in women with high baseline androgen levels (eg, PCOS), the respective elevations of androstenedione and testosterone may not be high enough to allow unequivocal diagnosis of androgen-producing gonadal tumors. In these cases, an elevation of the usual ratio of testosterone to androstenedione of 1, to a ratio of >1.5, is a strong indicator of neoplastic androgen production. Diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always requires the measurement of several steroids. Patients with CAH due to 21-hydroxylase gene (CYP21A2) mutations the most common cause of CAH (>90% of cases), usually have very high levels of androstenedione, often 5- to 10-fold elevations. OHPG levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. In the much less common CYP11A1 mutation, androstenedione levels are elevated to a similar extend as in CYP21A2 mutation, and cortisol is also low, but OHPG is only mildly, if at all, elevated. Also less common, 3 beta HSD-2 deficiency is characterized by low cortisol and substantial elevations in DHEA-S and 17-alpha-hydroxyprogrenolone, while androstenedione is either low, normal, or, rarely, very mildly elevated (as a consequence of peripheral tissue androstenedione production by 3 beta HSD-1). In the very rare STAR (steroidogenic acute regulatory protein) deficiency, all steroid hormone levels are low and cholesterol is elevated. In the also very rare 17-alpha-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxyprogrenolone, OHPG, DHEA-S), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid and their precursors, in particular progesterone, 11-deoxycorticosterone, corticosterone, and 18-hydroxycorticosterone, are increased. The goal of CAH treatment is normalization of cortisol levels and, ideally, also of sex-steroid levels. Traditionally, OHPG and urinary pregnanetriol or total ketosteroid excretion are measured to guide treatment, but these tests correlate only modestly with androgen levels. Therefore, androstenedione and
testosterone should also be measured and used for treatment modifications. Normal prepubertal levels may be difficult to achieve, but if testosterone levels are within the reference range, androstenedione levels up to 100 ng/dL are usually regarded as acceptable. Girls below the age of 7 to 8 and boys before age 8 to 9 who present with early development of pubic hair or, in boys, penile enlargement, may be suffering from either premature adrenarche or premature puberty, or both. Measurement of DHEA-S, DHEA, and androstenedione, alongside determination of sensitive estradiol, total and bioavailable or free testosterone, sex hormone binding globulin (SHBG), and luteinizing hormone/follicle-stimulating hormone levels will allow correct diagnosis in most cases. In premature adrenarche, only the adrenal androgens, chiefly DHEA-S, and to a lesser degree, androstenedione, will be above prepubertal levels, whereas early puberty will also show a fall in SHBG levels and variable elevations of gonadotropins and gonadal sex-steroids above the prepuberty reference range. See Steroid Pathways in Special Instructions.

**Reference Values:**

<table>
<thead>
<tr>
<th>Tanner Stages (prepubertal)</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
<th>Stage V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>Reference Range (ng/dL)</td>
<td>9.8-14.5</td>
<td>31-65</td>
<td>10.7-15.4</td>
<td>50-100</td>
</tr>
<tr>
<td>Stage I</td>
<td>Stage II</td>
<td>Stage III</td>
<td>Stage IV</td>
<td>Stage V</td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td>Reference Range (ng/dL)</td>
<td>11.8-16.2</td>
<td>48-140</td>
<td>12.8-17.3</td>
<td>65-210 Females*</td>
</tr>
</tbody>
</table>

**Clinical References:**

**Angiosarcoma, MYC (8q24) Amplification, FISH, Tissue**

**Clinical Information:** Postradiation cutaneous angiosarcoma is a malignancy associated with very poor outcome and is consequently treated aggressively. Conversely, atypical vascular lesions are also associated with radiation therapy, but are considered to be benign and do not require aggressive management. Therefore, the differentiation of these neoplasms is of considerable clinical importance. Postradiation cutaneous angiosarcomas are characterized by high-level amplification of MYC, whereas reactive and benign vascular lesions do not show amplification of MYC. Similar diagnostic difficulties arise in the setting of primary cutaneous vascular lesions. A subset of primary cutaneous angiosarcomas...
also shows high-level MYC amplification, which can be useful in the differentiation from benign primary cutaneous vascular lesions.

**Useful For:** Identifying MYC amplification to aid in the differentiation of cutaneous angiosarcomas from atypical vascular lesions after radiotherapy An aid in the diagnosis of primary cutaneous angiosarcoma

**Interpretation:** The MYC locus is reported as amplified when the MYC:D8Z2 ratio of 2.0 or greater and demonstrates 6 or more copies of the MYC locus. A lesion with a MYC:D8Z2 ratio <2.0 or showing a ratio of 2.0 or greater with less than 6 copies of MYC is considered to lack amplification of the MYC locus.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FACEC 57824**

*Angiotensin Converting Enzyme, CSF*

**Useful For:** Support diagnosis of neurosarcoidosis. May be used to evaluate treatment response.

**Reference Values:**
0.0-2.5 U/L

**ACE 8285**

*Angiotensin Converting Enzyme, Serum*

**Clinical Information:** Angiotensin converting enzyme (ACE) participates in the renin cascade in response to hypovolemia. Its peptidase action on the decapetide angiotensinogen I results in the hydrolysis of a terminal histidyl leucine dipeptide and the formation of the octapeptide angiotensin II, a potent vasoconstrictor that increases blood pressure. The primary source of ACE is the endothelium of the lung. ACE activity is increased in sarcoidosis, a systemic granulomatous disease that commonly affects the lungs. In sarcoidosis, ACE is thought to be produced by epithelioid cells and macrophages of the granuloma. Currently, it appears that ACE activity reflects the severity of sarcoidosis: 68% positivity in those with stage I sarcoidosis, 86% in stage II sarcoidosis, and 91% in stage III sarcoidosis. Serum ACE also appears to reflect the activity of the disease; there is a dramatic decrease in enzyme activity in some patients receiving prednisone. Other conditions such as Gaucher disease, leprosy, untreated hyperthyroidism, psoriasis, premature infants with respiratory distress syndrome, adults with amyloidosis, and histoplasmosis have been associated with increased levels of ACE.

**Useful For:** Evaluation of patients with suspected sarcoidosis

**Interpretation:** An elevation in the level of serum angiotensin converting enzyme (ACE), along with radiographic evidence of infiltrates or adenopathy and organ biopsies showing noncaseating epithelial granulomas is suggestive of a diagnosis of sarcoidosis. Serum ACE is significantly higher in most (approximately 80%) patients with active sarcoidosis. ACE is also elevated in a number of other diseases and in approximately 5% of the normal adult population.

**Reference Values:**
> or =18 years: 8-53 U/L

The reference interval for pediatric patients may be up to 50% higher than that of adults.

For SI unit Reference Values, see
https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html

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**Angiotensin I, Plasma**

**Clinical Information:** Angiotensin I is a ten amino acid peptide formed by Renin cleavage of Angiotensinogen (Renin Substrate). Angiotensin I has little biological activity except that high levels can stimulate Catecholamine production. It is metabolized to its biologically active byproduct Angiotensin II by Angiotensin Converting Enzyme (ACE). The formation of Angiotensin I is controlled by negative feedback of Angiotensin II and II on Renin release and by Aldosterone concentration. Levels of Angiotensin I are increased in many types of hypertension. Angiotensin I levels are used to determine Renin activity. Angiotensin I is excreted directly into the urine.

**Reference Values:**
Up to 25 pg/mL

This test was performed using a kit that has not been cleared or approved by the FDA and is designated as research use only. The analytic performance characteristics of this test have been determined by Inter Science Institute. This test is not intended for diagnosis or patient management decisions without confirmation by other medically established means.

---

**Angiotensin II, Plasma**

**Clinical Information:** Angiotensin II is an eight amino acid peptide formed by Angiotensin Converting Enzyme (ACE) cleavage of Angiotensin I. Angiotensin II is metabolized further to Angiotensin III. Angiotensin II release is controlled by Renin, blood pressure, blood volume, sodium balance and by Aldosterone concentration. Levels of Angiotensin II are increased in many types of hypertension. Angiotensin II stimulates the release of Anti-Diuretic Hormone, ACTH, Prolactin, Luteinizing Hormone, Oxytocin and Aldosterone. Angiotensin II increases vasoconstriction and inhibits tubular resorption of sodium, and can increase endothelial cell growth.

**Reference Values:**
10 - 60 pg/mL

This test was performed using a kit that has not been cleared or approved by the FDA and is designated as research use only. The analytic performance characteristics of this test have been determined by Inter Science Institute. This test is not intended for diagnosis or patient management decisions without confirmation by other medically established means.

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**Anisakis, Parasite, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and...
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Anise, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


FANSE 57520
Anatto Seed (Bixa orellana) IgE
**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 -0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:
<0.35 kU/L

ANNEX 70355
Annexin-1 Immunostain, Technical Component Only
**Clinical Information:** Annexin-1 (A1) was identified by gene expression profiling studies of hairy cell leukemia. In the appropriate context, positivity for annexin A1 favors a diagnosis of hairy cell leukemia. Normal granulocytes and precursors also express annexin A1, serving as a positive internal control in bone marrow specimens.

**Useful For:** Classification of leukemias

**Interpretation:** The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


ADNAS 80204
Anti-DNase B Titer, Serum
**Clinical Information:** A number of bacterial antigens have been identified in cultures of group A streptococci. These extracellular products are primarily enzymatic proteins and include streptolysin O, streptokinase, hyaluronidase, deoxyribonucleases (DNases A, B, C, and D), and nicotinamide adenine nucleotidase. Infections by the group A streptococci are unique because they can be followed by the serious nonpurulent complications of rheumatic fever and glomerulonephritis. Recent information
suggests that rheumatic fever is associated with infection by certain rheumatogenic serotypes (M1, M3, M5, M6, M18, and M19), while glomerulonephritis follows infection by nephritogenic serotypes (M2, M12, M49, M57, M59, and M60). Glomerulonephritis and rheumatic fever occur following the infection, after a period of latency following the infection, during which the patient is asymptomatic. The latency period for glomerulonephritis is approximately 10 days, and for rheumatic fever the latency period is 20 days.

**Useful For:** Demonstration of acute or recent streptococcal infection

**Interpretation:** Elevated values are consistent with an antecedent infection by group A streptococci. Although the antistreptolysin O (ASO) test is quite reliable, performing the anti-DNase is justified for 2 primary reasons. First, the ASO response is not universal. Elevated ASO titers are found in the sera of about 85% of individuals with rheumatic fever; ASO titers remain normal in about 15% of individuals with the disease. The same holds true for other streptococcal antibody tests: a significant portion of individuals with normal antibody titers for 1 test will have elevated antibody titers for another test. Thus, the percentage of false-negatives can be reduced by performing 2 or more antibody tests. Second, skin infections, in contrast to throat infections, are associated with a poor ASO response. Patients with acute glomerulonephritis following skin infection (post-impetigo) have an attenuated immune response to streptolysin O. For such patients, performance of an alternative streptococcal antibody test such as anti-DNase B is recommended.

**Reference Values:**
- <5 years: < or =250 U/mL
- 5-17 years: < or =375 U/mL
- > or =18 years: < or =300 U/mL


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**FAEAB 91854**

**Anti-Enterocyte Antibodies**

**Reference Values:**
- IgG: Negative
- IgA: Negative
- IgM: Negative

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**FAHMG 75157**

**Anti-HMGCR Autoantibodies**

**Clinical Information:** HMGCR Abs (3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase) are associated with necrotizing myopathy that is commonly related to statin exposure.

**Interpretation:** Anti-HMGCR antibodies are usually found in association with necrotizing myopathy related to statin therapy. However, about 30% of Anti-HMGCR positive patients with necrotizing myopathy have never been exposed to statins. The literature suggests that false positives are extremely rare. As a lab developed test (LDT), approval or clearance by the FDA is not required. This test may be used for clinical purposes and should not be regarded as investigational or for research. Diagnosis Number (%):

- Polymyositis/Dermatomyositis 2/76(2.6)
- Systemic Lupus Erythematosus 0/30(0.0)
- Primary Sjogren's Syndrome 0/30(0.0)
- Rheumatoid Arthritis 0/30(0.0)
- Systemic Sclerosis 0/30(0.0)
- Normal Controls 0/47(0.0)

**Reference Values:**
- Negative: <20
- Weak Positive: 20 â€“ 39
- Moderate Positive: 40 â€“ 59
- Strong Positive: >=60

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Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
**FIGA**

**Anti-IgA**

**Clinical Information:** For the evaluation of patients with recurrent infection for the possibility of IgA deficiency (IgAD). Patients with IgA deficiency may develop antibodies against IgA that make them susceptible to adverse reactions to blood products including intravenous immunoglobulin.

**Reference Values:**

<99 U/mL

Patients with IgG antibodies against IgA may suffer from anaphylactoid reactions when given IVIG that contains small quantities of IgA. In one study (Clinical Immunology 2007; 122;156) five out of eight patients with IgG anti-IgA antibodies developed anaphylactoid reactions when IVIG was administered.


**FANTI**

**Anti-IgE**

**Reference Values:**

Normal

This ELISA measures IgG antibodies specific for IgE. A result of normal indicates that the level of IgG anti-IgE antibodies is similar to that seen in a population of healthy individuals. A result of elevated indicates an increased level of IgG anti-IgE antibodies compared to healthy individuals. These autoantibodies have been implicated as a causative agent in autoimmune chronic urticaria and atopic dermatitis.

**FANBF**

**Anti-Nuclear Ab (FANA), Body Fluid**

**Reference Values:**

ANA Titer: <1:10

ANA Pattern: No Pattern

**FCLNE**

**Anti-Phosphatidylcholine Ab**

**Reference Values:**

Anti-Phosphatidylcholine IgA: <12.0 U/mL

Anti-Phosphatidylcholine IgG: <12.0 U/mL

Anti-Phosphatidylcholine IgM: <12.0 U/mL

Reference Range applies to Antiphosphatidylcholine IgA, IgG & IgM:

Normal <12.0

Equivocal 12.0 â€“ 18.0

Elevated >18.0
**Anti-Phosphatidylethanolamine Panel**

**Reference Values:**

- Anti-Phosphatidylethanolamine IgA
  - <12.0 U/mL
- Anti-Phosphatidylethanolamine IgG
  - <12.0 U/mL
- Anti-Phosphatidylethanolamine IgM
  - <12.0 U/mL

Reference Range applies to Antiphosphatidylethanolamine IgA, IgG, & IgM

- **Normal:** <12.0
- **Equivocal:** 12.0 – 18.0
- **Elevated:** >18.0

**Anti-retinal autoantibodies follow up, WB**

**Reference Values:**

A final report will be attached in MayoAccess.

**Antibody Identification, RBC**

**Clinical Information:** After exposure to foreign red blood cells via transfusion or pregnancy, some people form antibodies that are capable of the destruction of transfused red cells or of fetal red cells in utero. It is important to identify the antibody specificity in order to assess the antibody's capability of causing clinical harm and, if necessary, to avoid the antigen on transfused red blood cells. Autoantibodies react against the patient's own red cells as well as the majority of cells tested. Autoantibodies can be clinically benign or can hemolyze the patient's own red blood cells, such as in cold agglutinin disease or autoimmune hemolytic anemia.

**Useful For:** Assessing positive pretransfusion antibody screens, transfusion reactions, hemolytic disease of the newborn, and autoimmune hemolytic anemias. This test is not useful for monitoring the efficacy of Rh-immune globulin administration. This test is not useful for identifying antibodies detected only at 4 degrees C or only after extended room temperature incubation.

**Interpretation:** Specificity of alloantibodies will be stated. The patient's red blood cells will be typed for absence of the corresponding antigens or as an aid to identification in complex cases. A consultation service is offered, at no charge, regarding the clinical relevance of red cell antibodies.

**Reference Values:**

- **Negative:**
- If positive, antibodies will be identified and corresponding special red cell antigen typing on patient’s red blood cells will be performed.


**Antibody Screen with Reflexed Antibody Identification, RBC**

**Clinical Information:** Transfusion and pregnancy are the primary means of sensitization to red cell antigens. In a given population, 2% to 4% of the general population possess irregular red cell alloantibodies. Such antibodies may cause hemolytic disease of the newborn or hemolysis of transfused donor red blood cells.
Useful For: Detection of allo- or autoantibodies directed against red blood cell antigens in the settings of pretransfusion testing. Evaluation of transfusion reactions. Evaluation of hemolytic anemia.

Interpretation: A positive result (antibody detected) necessitates antibody identification to establish the specificity and clinical significance of the antibody detected. Alloantibodies detected on pregnant Mayo Clinic-Rochester patients will be evaluated for the allo-antibody titer. If antibody reacts strongly, the titre test will be performed. Negative results indicate no antibody was detected.

Reference Values:
Negative
If positive, antibody identification will be performed.


**Antibody Titer, RBC**

Clinical Information: Some maternal IgG alloantibodies to red blood cell antigens will cross the placenta and cause hemolysis of antigen-positive fetal red cells. The resulting fetal anemia and hyperbilirubinemia can be harmful or even fatal to the newborn.

Useful For: Monitoring antibody levels during pregnancy to help assess the risk of hemolytic disease of the newborn. This test is not useful for monitoring the efficacy of Rh-immune globulin administration.

Interpretation: The specificity of the maternal alloantibody will be stated. The titer result is the reciprocal of the highest dilution at which macroscopic agglutination (1+) is observed. If the antibody problem identified is not relevant in hemolytic disease of the newborn or if titrations are not helpful, the titer will be canceled and will be replaced by ABIDR / Antibody Identification, RBC. A consultation service is offered, at no charge, regarding the clinical relevance of red cell antibodies.

Reference Values:
Negative.
If positive, result will be reported as the reciprocal of the highest dilution at which macroscopic agglutination (1+) is observed.


**Antibody to Extractable Nuclear Antigen Evaluation, Serum**

Clinical Information: SSA, SSB, SM, and RNP are extractable nuclear antigens (ENA) that occur in patients with several different connective tissue diseases. Scl 70 (topoisomerase 1) is a 100-kD nuclear and nucleolar enzyme. Scl 70 antibodies are considered to be specific for scleroderma (systemic sclerosis) and are found in up to 60% of patients with this connective tissue disease. Scl 70 antibodies are more common in patients with extensive cutaneous involvement and interstitial pulmonary fibrosis, and are considered a poor prognostic sign. (1) JO1 is a member of the amino acyl-tRNA synthetase family of enzymes found in all nucleated cells and a marker for the disease polymyositis. For more information, see individual unit codes.

Useful For: Evaluating patients with signs and symptoms of a connective tissue disease in whom the test for antinuclear antibodies is positive.

Interpretation: A positive result is consistent with a connective tissue disease. For more information, see individual unit codes.

Reference Values:
SS-A/Ro ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

SS-B/La ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

Sm ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

RNP ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

Scl 70 ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.

Jo 1 ANTIBODIES, IgG
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.


FADDS 57772
Antidepressant Drug Screen, Qualitative
Reference Values:
Antidepressant screen includes the analysis for:
Amytriptyline, Clomipramine and Desmethylclomipramine, Cyclobenzaprine, Desipramine, Doxepin and Desmethyldoxepin, Fluoxetine and Norfluoxetine, Imipramine, Maprotiline, Nortriptyline, Paroxetine, Protriptyline, Sertraline and Desmethylsertraline, Trimipramine.

FASQN 57740
Antidepressant Drug Screen, Ur, Quantitative
Reference Values:
Antidepressant screen includes the analysis for: amitriptyline, clomipramine and desmethylclomipramine, cyclobenzaprine, desipramine, doxepin and desmethyldoxepin, fluoxetine and norfluoxetine, imipramine, maprotiline, nortriptyline, paroxetine, protriptyline, sertraline and desmethylsertraline, trimipramine.

MMLYP 81602
Antimicrobial Susceptibility Panel, Yeast
Clinical Information: Candida species are the fourth leading cause of nosocomial infections and are also frequent causes of community-acquired infections. Antifungal susceptibility testing may aid in the management of patients with invasive infections due to Candida species or patients who appear to be experiencing therapeutic failure. The Clinical Laboratory Standards Institute has approved the use of a
broth microdilution method for determining the susceptibility of Candida species.

**Useful For:** Determining in vitro quantitative antifungal susceptibility (minimum inhibitory concentration) of non-fastidious yeast. Testing may be warranted to aid in the management of certain circumstances, such as: -Refractory oropharyngeal infections due to Candida species in patients who appear to be experiencing therapeutic failure with standard agents at standard doses -Invasive infections due to Candida species when the utility of azole antifungal agents is uncertain (eg, when the infection is due to a non-Candida albicans organism)

**Interpretation:** The minimum inhibitory concentration (MIC) is recorded as the lowest concentration of antifungal agent producing complete inhibition of growth. Interpretive breakpoints are available for Candida albicans, Candida glabrata, Candida guilliermondii, Candida krusei, Candida parapsilosis, and Candida tropicalis for limited drugs (see tables below); the clinical relevance of testing any other organism-drug combination remains uncertain. Agent MIC Ranges on Yeast Plate (mcg/mL)

**Candida albicans Interpretations (mcg/mL)**

- Susceptible Dose Dependent
- Intermediate
- Resistant

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC Ranges (mcg/mL)</th>
<th>Interpretations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin</td>
<td>0.12-8</td>
<td></td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>0.015-8</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>0.125-256 &lt; or =2</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0.015-16</td>
<td></td>
</tr>
<tr>
<td>Micafungin</td>
<td>0.008-8</td>
<td></td>
</tr>
<tr>
<td>5-Flucytosine</td>
<td>0.06-64</td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>0.008-8</td>
<td></td>
</tr>
<tr>
<td>Caspofungin</td>
<td>0.008-8</td>
<td></td>
</tr>
</tbody>
</table>

**Candida glabrata Interpretations (mcg/mL)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC Ranges (mcg/mL)</th>
<th>Interpretations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin</td>
<td>0.12-8</td>
<td></td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>0.015-8</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>0.125-256 &lt; or =2</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0.015-16</td>
<td></td>
</tr>
<tr>
<td>Micafungin</td>
<td>0.008-8</td>
<td></td>
</tr>
<tr>
<td>5-Flucytosine</td>
<td>0.06-64</td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>0.008-8</td>
<td></td>
</tr>
</tbody>
</table>

**Candida guilliermondii Interpretations (mcg/mL)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC Ranges (mcg/mL)</th>
<th>Interpretations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin</td>
<td>0.12-8</td>
<td></td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>0.015-8</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>0.125-256 &lt; or =2</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0.015-16</td>
<td></td>
</tr>
<tr>
<td>Micafungin</td>
<td>0.008-8</td>
<td></td>
</tr>
<tr>
<td>5-Flucytosine</td>
<td>0.06-64</td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>0.008-8</td>
<td></td>
</tr>
</tbody>
</table>

**Candida krusei Interpretations (mcg/mL)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC Ranges (mcg/mL)</th>
<th>Interpretations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin</td>
<td>0.12-8</td>
<td></td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>0.015-8</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>0.125-256 &lt; or =2</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0.015-16</td>
<td></td>
</tr>
<tr>
<td>Micafungin</td>
<td>0.008-8</td>
<td></td>
</tr>
<tr>
<td>5-Flucytosine</td>
<td>0.06-64</td>
<td></td>
</tr>
</tbody>
</table>

**Candida parapsilosis Interpretations (mcg/mL)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC Ranges (mcg/mL)</th>
<th>Interpretations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin</td>
<td>0.12-8</td>
<td></td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>0.015-8</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>0.125-256 &lt; or =2</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0.015-16</td>
<td></td>
</tr>
<tr>
<td>Micafungin</td>
<td>0.008-8</td>
<td></td>
</tr>
<tr>
<td>5-Flucytosine</td>
<td>0.06-64</td>
<td></td>
</tr>
</tbody>
</table>

**Candida tropicalis Interpretations (mcg/mL)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC Ranges (mcg/mL)</th>
<th>Interpretations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin</td>
<td>0.12-8</td>
<td></td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>0.015-8</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>0.125-256 &lt; or =2</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0.015-16</td>
<td></td>
</tr>
<tr>
<td>Micafungin</td>
<td>0.008-8</td>
<td></td>
</tr>
<tr>
<td>5-Flucytosine</td>
<td>0.06-64</td>
<td></td>
</tr>
</tbody>
</table>

Please note that Candida krusei is intrinsically resistant to fluconazole regardless of the in vitro MIC result.

**Reference Values:**

Results reported in mcg/mL.


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**Antimicrobial Susceptibility, Acid-Fast Bacilli, Rapidly Growing**

**Clinical Information:** The rapidly growing species of mycobacteria (eg, Mycobacterium fortuitum, Mycobacterium peregrinum, Mycobacterium chelonae, Mycobacterium abscessus, and Mycobacterium mucogenicum) are seen with increasing frequency as causes of infection. Some examples of infections...
caused by this group of mycobacteria are empyema, subcutaneous abscess, cutaneous ulcerative and nodular lesions, peritonitis, endometriosis, bacteremia, keratitis, and urinary tract, prosthetic joint, wound, and disseminated infections. Rapidly growing mycobacteria differ from other species of mycobacteria by their growth rates, metabolic properties, and antimicrobial susceptibility profiles. Most species are susceptible to some of the traditional antimycobacterial agents, but rapidly growing species may exhibit resistance to certain antimycobacterial agents. In contrast, they often are susceptible to several of the antibacterial agents used to treat common bacterial infections. Therefore, the antimicrobial susceptibility profile of an organism within this group varies depending on the species. Antimicrobials tested in this assay are amikacin, cefoxitin, ciprofloxacin, clarithromycin, doxycycline, imipenem, tobramycin, trimethoprim/sulfamethoxazole, linezolid, moxifloxacin, minocycline and tigecycline.

**Useful For:** Determination of resistance of rapidly growing mycobacteria to antimicrobial agents

**Interpretation:** Results are reported as the minimum inhibitory concentration in micrograms/mL.

**Reference Values:**

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Susceptible (mcg/mL)</th>
<th>Intermediate (mcg/mL)</th>
<th>Resistant (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>&lt; or =16</td>
<td>32</td>
<td>&gt; or =64</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>&lt; or =16</td>
<td>32-64</td>
<td>&gt; or =128</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&lt; or =1.0</td>
<td>2.0</td>
<td>&gt; or =4.0</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>&lt; or =2.0</td>
<td>4.0</td>
<td>&gt; or =8.0</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>&lt; or =1.0</td>
<td>2.0-8.0</td>
<td>&gt; or =16</td>
</tr>
<tr>
<td>Imipenem</td>
<td>&lt; or =4.0</td>
<td>8.0</td>
<td>&gt; or =16</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&lt; or =2.0</td>
<td>4.0</td>
<td>&gt; or =8</td>
</tr>
<tr>
<td>Linezolid</td>
<td>&lt; or =8.0</td>
<td>16</td>
<td>&gt; or =32</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole</td>
<td>&lt; or =2/38</td>
<td>-</td>
<td>&gt; or =4/76</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>&lt; or =1.0</td>
<td>2.0</td>
<td>&gt; or =4.0</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>No interpretations available</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinical References:**
2. Colombo RE, Olivier KN: Diagnosis and treatment of infections caused by rapidly growing mycobacteria. Semin Respir Crit Care Med 2008 October;29:577-588

**Antimicrobial Susceptibility, Acid-Fast Bacilli, Slowly Growing Clinical Information:** There are currently more than 60 recognized, validated species of slowly growing nontuberculous mycobacteria and they are associated with a variety of infections including pulmonary, extrapolmonary, and disseminated disease. Slowly growing mycobacteria differ from the rapidly growing mycobacteria and Mycobacterium tuberculosis complex by their growth rates, metabolic properties, and antimicrobial susceptibility profiles. The antimicrobial susceptibility profile of an organism within this group varies depending on the species and is performed according to the Clinical and Laboratory Standards Institute (CLSI) guideline for slowly growing mycobacteria. The antimicrobial agents tested for each species or group are as follows: Mycobacterium avium Complex: Clarithromycin is tested and is the CLSI recommended primary agent. Moxifloxacin and linezolid are tested and are secondary agents with recommended CLSI breakpoints. Other recognized secondary drugs tested and reported without CLSI interpretive breakpoints are amikacin, ethambutol, rifampin, rifabutin, and streptomycin. Mycobacterium kansasi, Mycobacterium malmoense, Mycobacterium simiae,
Mycobacterium terrae, and Mycobacterium xenopi: Clarithromycin and rifampin are tested and are the CLSI recommended primary agents. Amikacin, ciprofloxacin, ethambutol, linezolid, moxifloxacin, rifabutin, and trimethoprim/sulfamethoxazole are tested and are secondary agents with recommended CLSI breakpoints. Isoniazid and streptomycin are tested and are secondary agents per CLSI but do not have recommended breakpoints. Mycobacterium malmoense can be difficult to grow in the test medium so some isolates may not be amenable to testing. Mycobacterium marinum: CLSI recommended agents tested are amikacin, ciprofloxacin, clarithromycin, doxycycline/minocycline, ethambutol, moxifloxacin, rifabutin, rifampin, and trimethoprim/sulfamethoxazole. Mycobacterium gordonae: Mycobacterium gordonae is frequently encountered in the environment and in clinical laboratories but is almost always considered nonpathogenic; therefore, antimicrobial susceptibility testing for Mycobacterium gordonae is performed by specific request only. Other slowly growing mycobacterial species: All other slowly growing mycobacterial species will be tested against the Mycobacterium kansasii panel of drugs and minimum inhibitory concentration values will be provided using the Mycobacterium kansasii interpretative criteria. The extremely fastidious slowly growing mycobacteria (Mycobacterium genavense and Mycobacterium haemophilum) will not be tested.

**Useful For:** Determination of resistance of slowly growing mycobacteria to antimicrobial agents

**Interpretation:** Results are reported as the minimum inhibitory concentration in micrograms/mL.

**Reference Values:**

**Interpretive Criteria for Mycobacterium avium-intracellulare complex**

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>MIC (mcg/mL) for each interpretation</th>
<th>S</th>
<th>I</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>≤ or =8</td>
<td>16</td>
<td>&gt; or =32</td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>≤ or =8</td>
<td>16</td>
<td>&gt; or =32</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>≤ or =1</td>
<td>2</td>
<td>&gt; or =4</td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>No Interpretations available</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>No Interpretations available</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin</td>
<td>No Interpretations available</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>No Interpretations available</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>No Interpretations available</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Interpretative criteria for Mycobacterium kansasii and other slowly growing mycobacteria**

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>MIC (mcg/mL) for each interpretation</th>
<th>S</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>≤ or =32</td>
<td>&gt;32</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≤ or =2</td>
<td>&gt;2</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>≤ or =16</td>
<td>&gt;16</td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>≤ or =4</td>
<td>&gt;4</td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>No Interpretations available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>≤ or =16</td>
<td>&gt;16</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>≤ or =2</td>
<td>&gt;2</td>
<td></td>
</tr>
<tr>
<td>Rifabutin</td>
<td>≤ or =2</td>
<td>&gt;2</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>≤ or =1</td>
<td>&gt;1</td>
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</tr>
<tr>
<td>Streptomycin</td>
<td>No Interpretations available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim/ Sulfamethoxazole</td>
<td>≤ or =2/38</td>
<td>&gt;2/38</td>
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</tbody>
</table>
### Interpretative criteria for Mycobacterium marinum

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>MIC (mcg/mL) for each interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
</tr>
<tr>
<td>Amikacin</td>
<td>&lt; or =32</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&lt; or =2</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>&lt; or =16</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>&lt; or =4</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>&lt; or =4</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>&lt; or =2</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>&lt; or =2</td>
</tr>
<tr>
<td>Rifampin</td>
<td>&lt; or =1</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole</td>
<td>&lt; or =2/38</td>
</tr>
</tbody>
</table>

### Clinical References:
interpretations."

Susceptible (S):
A category defined by a breakpoint that implies that isolates with an MIC at or below the susceptible breakpoint are inhibited by the usually achievable concentrations of antimicrobial agent when the dosage recommended to treat the site of infection is used, resulting in likely clinical efficacy.

Susceptible-Dose Dependent (SDD):
A category defined by a breakpoint that implies that susceptibility of an isolate is dependent on the dosing regimen that is used in the patient. In order to achieve levels that are likely to be clinically effective against isolates for which the susceptibility testing results are in the SDD category, it is necessary to use a dosing regimen (ie, higher doses, more frequent doses, or both) that results in higher drug exposure than the dose that was used to establish the susceptible breakpoint. Consideration should be given to the maximum approved dosage regimen, because higher exposure gives the highest probability of adequate coverage of a SDD isolate. The drug label should be consulted for recommended doses and adjustment for organ function.

Intermediate (I):
A category defined by a breakpoint that includes isolates with MICs within the intermediate range that approach usually attainable blood and tissue levels and for which response rates may be lower than for susceptible isolates.
Note: The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated or when a higher than normal dosage of a drug can be used. This category also includes a buffer zone, which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.

Resistant (R):
A category defined by a breakpoint that implies that isolates with an MIC at or above the resistant breakpoint are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or that demonstrate MICs that fall in the range in which specific microbial resistance mechanisms are likely, and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.

Nonsusceptible (NS):
A category used for isolates for which only a susceptible breakpoint is designated because of the absence or rare occurrence of resistant strains. Isolates for which the antimicrobial agent MICs are above the value indicated for the susceptible breakpoint are reported as nonsusceptible.
Note: An isolate that is interpreted as nonsusceptible does not necessarily mean that the isolate has a resistance mechanism. It is possible that isolates with MICs above the susceptible breakpoint that lack resistance mechanisms may be encountered within the wild-type distribution subsequent to the time the susceptible-only breakpoint was set.

Epidemiological Cutoff Value (ECV):
The minimum inhibitory concentration (MIC) that separates microbial populations into those with and without acquired resistance (non-wild-type or wild-type, respectively). The ECV defines the highest MIC for the wild type population of isolates. ECVs are based on in vitro data only, using MIC distributions. ECVs are not clinical breakpoints, and the clinical relevance of ECVs for a particular patient has not yet been identified or approved by Clinical and Laboratory Standards Institute (CLSI) or any regulatory agency.

When an ECV is reported, the following comment will be included: "This MIC is consistent with the Epidemiological Cutoff Value (ECV) observed in isolates (WITH / WITHOUT) acquired resistance; however, correlation with treatment outcome is unknown."(Clinical and Laboratory Standards Institute: Performance Standards for Antimicrobial Susceptibility Testing. 28th edition. CLSI Supplement M100. Wayne, PA, 2018)

Antimicrobial Susceptibility, Anaerobic Bacteria, MIC

Clinical Information: Anaerobic bacteria are the greatest component of the human body’s normal flora and generally do not cause infection. When usual skin and mucosal barriers are penetrated and in an anaerobic environment, these bacteria can behave as pathogens. Anaerobes grow aggressively in the body under anaerobic conditions and may possess a variety of virulence factors including capsules and extracellular enzymes. They also can develop resistance to antimicrobials by producing beta-lactamase and other modifying enzymes and by alterations in membrane permeability and structure of penicillin-binding proteins. Because anaerobic bacteria are a significant cause of human infection and they are often resistant to commonly used antimicrobials, susceptibility testing results are useful to clinicians. Bacteroides species produce beta-lactamases. Ertapenem, metronidazole, and clindamycin are effective agents, although resistance to clindamycin, and occasionally ertapenem, is increasing. The minimum inhibitory concentration (MIC) obtained during antimicrobial susceptibility testing is helpful in indicating the concentration of antimicrobial agent required at the site of infection necessary to inhibit the infecting organism. The MICs are accompanied by interpretive categories (ie, susceptible, intermediate, or resistant) when applicable.

Useful For: Determining the in vitro susceptibility of anaerobic bacteria involved in human infections

Interpretation: A "susceptible" category result and a low minimum inhibitory concentration value indicate in vitro susceptibility of the organism to the antimicrobial tested. Refer to the Reference Values section for interpretation of various antimicrobial categories.

Reference Values:
Results are reported as minimum inhibitory concentration (MIC) in mcg/mL. Breakpoints (also known as “clinical breakpoints”) are used to categorize an organism as susceptible, susceptible-dose dependent, intermediate, resistant, or nonsusceptible according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.

Susceptible (S):
A category defined by a breakpoint that implies that isolates with an MIC at or below the susceptible breakpoint are inhibited by the usually achievable concentrations of antimicrobial agent when the dosage recommended to treat the site of infection is used, resulting in likely clinical efficacy.

Intermediate (I):
A category defined by a breakpoint that includes isolates with MICs within the intermediate range that approach usually attainable blood and tissue levels and for which response rates may be lower than for susceptible isolates.

Resistant (R):
A category defined by a breakpoint that implies that isolates with an MIC at or above the resistant breakpoint are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or that demonstrate MICs that fall in the range in which specific microbial resistance
mechanisms are likely, and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.

Epidemiological Cutoff Value (ECV):
The MIC that separates microbial populations into those with and without acquired resistance (non-wild-type or wild-type, respectively). The ECV defines the highest MIC for the wild type population of isolates. ECVs are based on in vitro data only, using MIC distributions. ECVs are not clinical breakpoints, and the clinical relevance of ECVs for a particular patient has not yet been identified or approved by CLSI or any regulatory agency.

When an ECV is reported, the following comment will be included: “This MIC is consistent with the Epidemiological Cutoff Value (ECV) observed in isolates [WITH/WITHOUT] acquired resistance; however, correlation with treatment outcome is unknown.”


Antimicrobial Susceptibility, Mycobacterium tuberculosis Complex, First Line

Clinical Information: Primary treatment regimens for Mycobacterium tuberculosis complex often include isoniazid, rifampin, ethambutol, and pyrazinamide. Susceptibility testing of each M tuberculosis complex isolate against these first-line antimycobacterial agents is a key component of patient management. In vitro susceptibility testing methods are available to assess the susceptibility of M tuberculosis complex isolates to selected antimycobacterial agents. The Clinical Laboratory Standards Institute (CLSI) provides consensus protocols for the methods, antimycobacterial agents, and critical concentrations of each agent to be tested in order to permit standardized interpretation of Mm tuberculosis complex susceptibility testing results. Current recommendations indicate that laboratories should use a rapid broth method in order to obtain M tuberculosis susceptibility data as quickly as possible to help guide patient management. Resistance, as determined by rapid testing, must be confirmed by another method or by another laboratory. This test uses an FDA-cleared commercial system for rapid broth susceptibility testing of M tuberculosis complex and assesses resistance to antimycobacterial drugs at the critical concentrations.

Useful For: Rapid, qualitative susceptibility testing of Mycobacterium tuberculosis complex isolates growing in pure culture Affirming the initial choice of chemotherapy for M tuberculosis infections Confirming the emergence of drug resistance Guiding the choice of alternate agents for therapy for M tuberculosis infections

Interpretation: Mycobacterium tuberculosis complex isolates are reported as susceptible or resistant to the aforementioned drugs at the critical concentrations. Some experts believe that patients infected with strains exhibiting resistance to low levels of isoniazid (0.1 mcg/mL) but not exhibiting resistance to high levels (0.4 mcg/mL) may benefit from continuing therapy with this agent. A specialist in the treatment of tuberculosis should be consulted concerning the appropriate therapeutic regimen and dosages.

Reference Values: Results are reported as susceptible or resistant.

Antimicrobial Susceptibility, Nocardia species

Clinical Information: Nocardia asteroides, the most commonly recognized aerobic actinomycete, causes significant disease in immunocompromised patients. Clinical presentations can include pneumonia, skin abscess, bacteremia, brain abscess, eye infection, and joint infection. Other species associated with human disease include Nocardia brasiliensis, Nocardia otitidiscaviarum, Nocardia farcinica, Nocardia nova, and Nocardia transvalensis. Treatment usually consists of trimethoprim-sulfamethoxazole, sometimes in combination with other antimicrobials, such as amikacin. However, some patients develop drug allergy, others develop resistant isolates due to noncompliance, and some antimicrobials penetrate the central nervous system better than others. Therefore, the selection of appropriate agents becomes extremely important to patient outcome.

Useful For: Determining the resistance of species of Nocardia and other aerobic actinomycetes to antimicrobial agents

Interpretation: Interpretive values for susceptibility testing of Nocardia species using a broth microdilution method. (Values expressed in mcg/mL): Antimicrobial Agent Interpretations S I R

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>Concentration Range mcg/mL</th>
<th>Interpretations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim/Sulfamethoxazole(3)</td>
<td>0.25/4.75-8/152</td>
<td>&lt; or =2/38 - &gt; or =4/76</td>
</tr>
<tr>
<td>Linezolid(2)</td>
<td>1-32</td>
<td>&lt; or =8 - -</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.12-4</td>
<td>&lt; or =1 2 &gt; or =4</td>
</tr>
<tr>
<td>Imipenem</td>
<td>2-64</td>
<td>&lt; or =4 8 &gt; or =16</td>
</tr>
<tr>
<td>Moxifloxacin(1,3)</td>
<td>0.25-8</td>
<td>- &gt; or =16</td>
</tr>
<tr>
<td>Cefepime(3)</td>
<td>1-32</td>
<td>&lt; or =8 16 &gt; or =32</td>
</tr>
<tr>
<td>Augmentin(3)</td>
<td>2/1-64/32</td>
<td>&lt; or =8/4 16/8 &gt; or =32/16</td>
</tr>
<tr>
<td>Amikacin</td>
<td>1-64</td>
<td>&lt; or =8 16-32 &gt; or =64</td>
</tr>
<tr>
<td>Ceftriaxone(3)</td>
<td>4-64</td>
<td>&lt; or =8 16-32 &gt; or =64</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>0.12-16</td>
<td>&lt; or =1 2-4 &gt; or =8</td>
</tr>
<tr>
<td>Minocycline(3)</td>
<td>1-8</td>
<td>&lt; or =1 2-4 &gt; or =8</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>1-16</td>
<td>&lt; or =4 8 &gt; or =16</td>
</tr>
</tbody>
</table>

Reference Values:

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Clarithromycin 0.06-16 < or =2 4 > or =8 For Rhodococcus equi, the interpretive criteria indicated in CLSI document M100 for Staphylococcus aureus are used for vancomycin and rifampin. The interpretive categories should be considered tentative pending accumulation of further information.

**Clinical References:**

**SBWB 64273 Antimony, Blood**

**Clinical Information:** Antimony is a silvery white metal that is used in alloys for lead batteries, solder, sheet metal, bearings, castings, ammunition, and pewter. It is also used for pigments, abrasives, flame-proofing fabrics, and in medications (ie, sodium stibogluconate [Pentostam], which is used to treat cutaneous leishmaniasis). (1) Antimony typically enters the environment during mining, processing of ores, emissions from coal-burning power plants, and production of alloys. Exposure to antimony can occur through inhalation, ingestion, or dermal contact with soil, water, foods, or medications that contain it. In the workplace, exposure is usually via inhalation. The Occupational Safety and Health Administration (OSHA) has set a limit of 0.5 mg/m3 of antimony in workroom air to protect workers during an 8-hour work shift (40-hour workweek). (2) Absorption of antimony through the lungs may take days to weeks. Absorption of antimony from ingestion typically enters the blood within a few hours. (2) The amount and form of the antimony affects how much is absorbed. Once in the blood, antimony is then distributed to the liver, lungs, intestines, and spleen. Elimination is primarily through the urine over several weeks. The half-life varies with the chemical form. Trivalent antimony is primarily bound to erythrocytes, while pentavalent antimony is primarily found in plasma, which makes whole blood the preferred specimen to analyze for acute intoxication. Whole blood concentrations in healthy subjects not exposed to antimony averaged 0.7 mcg/L and usually don’t exceed 2 mcg/L. (3) In battery plant workers, median blood antimony concentrations of 2.6 mcg/L were found in metal casters and 10 mcg/L in metal formers. (4) The effects of acute or chronic antimony poisoning are similar to arsenic and include abdominal pain, dyspnea, nausea, vomiting, dermatitis, and visual disturbances. (1) Additionally, toxicity can include pneumoconiosis, and altered electrocardiograms. (2)

**Useful For:** Determining antimony toxicity

**Interpretation:** Normal blood concentrations are 0.7 to 2 ng/mL in the unexposed, and 2.6 to 10 ng/mL in exposed workers. (3)

**Reference Values:**
- <2 ng/mL (unexposed)
- 3-10 ng/mL (exposed)

**Clinical References:**
Antimullerian Hormone (AMH), Serum

**Clinical Information:** Antimullerian hormone (AMH), also known as mullerian-inhibiting substance, is a dimeric glycoprotein hormone belonging to the transforming growth factor-beta family. It is produced by Sertoli cells of the testis in males and by ovarian granulosa cells in females. Expression during male fetal development prevents the müllerian ducts from developing into the uterus, resulting in development of the male reproductive tract. In the absence of AMH, the müllerian ducts and structures develop into the female reproductive tract. In males, AMH serum concentrations are elevated in males under 2 years old and then progressively decrease until puberty, when there is a sharp decline. In females, AMH is produced by the granulosa cells of small growing follicles from the 36th week of gestation onwards until menopause when levels become undetectable. Because of the gender differences in AMH concentrations, its changes in circulating concentrations with sexual development, and its specificity for Sertoli and granulosa cells, measurement of AMH has utility in the assessment of gender, gonadal function, fertility, and as a gonadal tumor marker. Since AMH is produced continuously in the granulosa cells of small follicles during the menstrual cycle, it is superior to the episodically released gonadotropins and ovarian steroids as a marker of ovarian reserve. Furthermore, AMH concentrations are unaffected by pregnancy or use of oral or vaginal estrogen- or progestin-based contraceptives. Studies in fertility clinics have shown that females with higher concentrations of AMH have a better response to ovarian stimulation and tend to produce more retrievable oocytes than females with low or undetectable AMH. Females at risk of ovarian hyperstimulation syndrome after gonadotropin administration can have significantly elevated AMH concentrations. Polycystic ovarian syndrome can elevate serum AMH concentrations because it is associated with the presence of large numbers of small follicles. AMH measurements are commonly used to evaluate testicular presence and function in infants with intersex conditions or ambiguous genitalia, and to distinguish between cryptorchidism (testicles present but not palpable) and anorchia (testicles absent) in males. In minimally virilized phenotypic females, AMH helps differentiate between gonadal and nongonadal causes of virilization. Serum AMH concentrations are increased in some patients with ovarian granulosa cell tumors, which comprise approximately 10% of ovarian tumors. AMH, along with related tests including inhibin A and B (INHA / Inhibin A, Tumor Marker, Serum; INHB / Inhibin B, Serum; INHAB / Inhibin A and B, Tumor Marker, Serum), estradiol (EEST / Estradiol, Serum), and CA-125 (CA25 / Cancer Antigen 125 [CA 125], Serum), can be useful for diagnosing and monitoring these patients.

**Useful For:** Assessment of menopausal status, including premature ovarian failure Assessing ovarian status, including ovarian reserve and ovarian responsiveness, as part of an evaluation for infertility and assisted reproduction protocols such as in vitro fertilization Assessing ovarian function in patients with polycystic ovarian syndrome Evaluation of infants with ambiguous genitalia and other intersex conditions Evaluating testicular function in infants and children Monitoring patients with antimullerian hormone-secreting ovarian granulosa cell tumors

**Interpretation:** Menopausal women or women with premature ovarian failure of any cause, including after cancer chemotherapy, have very low antimullerian hormone (AMH) levels, often below the current assay detection limit of 0.1 ng/mL. While the optimal AMH concentrations for predicting response to in vitro fertilization are still being established, it is accepted that AMH concentrations in the perimenopausal to menopausal range indicate minimal to absent ovarian reserve. Depending on patient age, ovarian stimulation is likely to fail in such patients By contrast, if serum AMH concentrations exceed 3 ng/mL, hyper-response to ovarian stimulation may result. For these patients, a minimal stimulation would be recommended. In patients with polycystic ovarian syndrome, AMH concentrations may be 2- to 5-fold higher than age-appropriate reference range values. Such high levels predict anovulatory and irregular cycles. In children with intersex conditions, an AMH result above the normal female range is predictive of the presence of testicular tissue, while an undetectable value suggests its absence. In boys with cryptorchidism, a measurable AMH concentration is predictive of undescended testes, while an
undetectable value is highly suggestive of anorchia or functional failure of the abnormally sited gonad. Granulosa cell tumors of the ovary may secrete AMH, inhibin A, and inhibin B. Elevated levels of any of these markers can indicate the presence of such a neoplasm in a woman with an ovarian mass. Levels should fall with successful treatment. Rising levels indicate tumor recurrence or progression.

Reference Values:
Males
- <24 months: 14-466 ng/mL
- 24 months-12 years: 7.4-243 ng/mL
- >12 years: 0.7-19 ng/mL
Females
- <24 months: <4.7 ng/mL
- 24 months-12 years: <8.8 ng/mL
- 13-45 years: 0.9-9.5 ng/mL
- >45 years: <1.0 ng/mL

Clinical References:

VASC 83012
Antineutrophil Cytoplasmic Antibodies Vasculitis Panel, Serum

Clinical Information: Antineutrophil cytoplasmic antibodies (ANCA) occur in patients with autoimmune vasculitis including Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), or organ-limited variants thereof such as pauci-immune necrotizing glomerulonephritis.(1) ANCA react with enzymes in the cytoplasmic granules of human neutrophils including proteinase 3 (PR3), myeloperoxidase (MPO), elastase, and cathepsin G. Autoantibodies to PR3 occur in patients with WG (both classical WG and WG with limited end-organ involvement) and produce a characteristic pattern of granular cytoplasmic fluorescence on ethanol-fixed neutrophils called the cANCA pattern. Antibodies to MPO occur predominately in patients with MPA and produce a pattern of perinuclear cytoplasmic fluorescence on ethanol-fixed neutrophils called the pANCA pattern. Autoantibodies to PR3 and MPO can also be detected by EIA methods and are referred to as PR3 ANCA and MPO ANCA, respectively.

Useful For: Evaluating patients suspected of having autoimmune vasculitis, both Wegener's and microscopic polyangiitis

Interpretation: Positive results for proteinase 3 (PR3) antineutrophil cytoplasmic antibodies (ANCA) and cANCA or pANCA are consistent with the diagnosis of Wegener's granulomatosis (WG), either systemic WG with respiratory and renal involvement or limited WG with more restricted end-organ involvement. Positive results for MPO ANCA and pANCA are consistent with the diagnosis of autoimmune vasculitis including microscopic polyangiitis (MPA) or pauci-immune necrotizing glomerulonephritis. A positive result for PR3 ANCA or MPO ANCA has been shown to detect 89% of patients with active WG or MPA (with or without renal involvement) with fewer than 1% false-positive results in patients with other diseases.(1)

Reference Values:
MYELOPEROXIDASE ANTIBODIES, IgG
- <0.4 U (negative)
- 0.4-0.9 U (equivocal)
- > or =1.0 U (positive)
Reference values apply to all ages.

PROTEINASE 3 ANTIBODIES, IgG
- <0.4 U (negative)
- 0.4-0.9 U (equivocal)
- > or =1.0 U (positive)
Reference values apply to all ages.


### ANA2

#### Antinuclear Antibodies (ANA), Serum

**Clinical Information:** Measurement of antinuclear antibodies (ANAs) in serum is the most commonly performed screening test for patients suspected of having a systemic rheumatic disease, also referred to as connective tissue disease.(1) ANAs occur in patients with a variety of autoimmune diseases, both systemic and organ-specific. They are particularly common in the systemic rheumatic diseases, which include lupus erythematosus (LE), discoid LE, drug-induced LE, mixed connective tissue disease, Sjogren syndrome, scleroderma (systemic sclerosis), CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, telangiectasia) syndrome, polymyositis/dermatomyositis, and rheumatoid arthritis.(1) The diagnosis of a systemic rheumatic disease is based primarily on the presence of compatible clinical signs and symptoms. The results of tests for autoantibodies including ANA and specific autoantibodies are ancillary. Additional diagnostic criteria include consistent histopathology or specific radiographic findings. Although individual systemic rheumatic diseases are relatively uncommon, a great many patients present with clinical findings that are compatible with a systemic rheumatic disease and large numbers of tests for ANA are ordered to eliminate the possibility of a systemic rheumatic disease. See Connective Tissue Diseases Cascade Test-Ordering Algorithm in Special Instructions.

**Useful For:** Evaluating patients suspected of having a systemic rheumatic disease

**Interpretation:** A large number of healthy individuals have weakly-positive antinuclear antibody (ANA) results, many of which are likely to be clinical false-positives; therefore, second-order testing of all positive ANAs yields a very low percentage of positive results to the specific nuclear antigens. A positive ANA result at any level is consistent with the diagnosis of systemic rheumatic disease, but a result greater than or equal to 3.0 U is more strongly associated with systemic rheumatic disease than a weakly-positive result. Positive ANA results greater than 3.0 U are associated with the presence of detectable autoantibodies to specific nuclear antigens. The nuclear antigens are associated with specific diseases (eg, anti-Scl 70 is associated with scleroderma) and can be detected with second-order testing.

**Reference Values:**

- < or =1.0 U (negative)
- 1.1-2.9 U (weakly positive)
- 3.0-5.9 U (positive)
- > or =6.0 U (strongly positive)

Reference values apply to all ages.


### NAIFA

#### Antinuclear Antibodies, HEp-2 Substrate, IgG, Serum

**Clinical Information:** Measurement of antinuclear antibodies (ANA) in serum is the most commonly performed screening test for patients suspected of having a systemic rheumatic disease, also referred to as connective tissue disease.(1) ANA occur in patients with a variety of autoimmune diseases, both systemic and organ-specific. They are particularly common in the systemic rheumatic diseases, which include lupus erythematous (LE), discoid LE, drug-induced LE, mixed connective tissue disease, Sjogren syndrome, scleroderma (systemic sclerosis), CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility,
sclerodactyly, telangiectasia) syndrome, polymyositis/dermatomyositis, and rheumatoid arthritis.(1) The diagnosis of a systemic rheumatic disease is based primarily on the presence of compatible clinical signs and symptoms. The results of tests for autoantibodies including ANA and specific autoantibodies are ancillary. Additional diagnostic criteria include consistent histopathology or specific radiographic findings. Although individual systemic rheumatic diseases are relatively uncommon, a great many patients present with clinical findings that are compatible with a systemic rheumatic disease and large numbers of tests for ANA are ordered to eliminate the possibility of a systemic rheumatic disease.

**Useful For:** Evaluating patients suspected of having systemic rheumatic disease

**Interpretation:** A large number of healthy individuals have low titer antinuclear antibody (ANA) results, many of which are likely to be clinical false-positives; therefore, second-order testing of all positive ANAs yields a very low percentage of positive results to the specific nuclear antigens. A positive ANA result at any level is consistent with the diagnosis of systemic rheumatic disease. Positive ANA results are associated with the presence of detectable autoantibodies to specific nuclear antigens. The nuclear antigens are associated with specific diseases (eg, anti-Scl 70 is associated with scleroderma) and can be detected with second-order testing.

**Reference Values:**
<1:80 (Negative)

**Clinical References:**

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**Antistrep-O Titer, Serum**

**Clinical Information:** A number of bacterial antigens have been identified in cultures of group A streptococci. These extracellular products are primarily enzymatic proteins and include streptolysin O, streptokinase, hyaluronidase, deoxyribonucleases (DNases A, B, C, and D), and nicotinamide adenine nucleotidase. Infections by the group A streptococci are unique because they can be followed by the serious nonpurulent complications of rheumatic fever and glomerulonephritis. Recent information suggests that rheumatic fever is associated with infection by certain rheumatogenic serotypes (M1, M3, M5, M6, M18, and M19), while glomerulonephritis follows infection by nephritogenic serotypes (M2, M12, M49, M57, M59, and M60). Glomerulonephritis and rheumatic fever occur following the infection, after a period of latency following the infection, during which the patient is asymptomatic. The latency period for glomerulonephritis is approximately 10 days, and for rheumatic fever the latency period is 20 days.

**Useful For:** Demonstration of acute or recent streptococcal infection

**Interpretation:** Elevated values are consistent with an antecedent infection by group A streptococci. Although the antistreptolysin O (ASO) test is quite reliable, performing the anti-DNase is justified for 2 primary reasons. First, the ASO response is not universal. Elevated ASO titers are found in the sera of about 85% of individuals with rheumatic fever; ASO titers remain normal in about 15% of individuals with the disease. The same holds true for other streptococcal antibody tests: a significant portion of individuals with normal antibody titers for 1 test will have elevated antibody titers for another test. Thus, the percentage of false-negatives can be reduced by performing 2 or more antibody tests. Second, skin infections, in contrast to throat infections, are associated with a poor ASO response. Patients with acute glomerulonephritis following skin infection (post-impetigo) have an attenuated immune response to streptolysin O. For such patients, performance of an alternative streptococcal antibody test such as anti-DNase B is recommended.

**Reference Values:**
<5 years: < or =70 IU/mL
5-17 years: < or =640 IU/mL
> or =18 years: < or =530 IU/mL
Antithrombin Activity, Plasma

Clinical Information: Antithrombin is a member of the serine protease inhibitor (serpin) superfamily. It is the principal plasma anticoagulant serpin mediating inactivation of serine protease procoagulant enzymes, chiefly thrombin and coagulation factors Xa and IXa. Heparin and certain other naturally occurring glycosaminoglycans markedly enhance antithrombin’s anticoagulant activity (approximately 1,000-fold) by providing a template to catalyze formation of covalently bonded, inactive complexes of serine protease and antithrombin that are subsequently cleared from circulation. Antithrombin is the mediator of heparin’s anticoagulant activity. The antithrombin gene on chromosome 1 encodes a glycoprotein of approximately 58,000 molecular weight that is synthesized in the liver and is present in a relatively high plasma concentration (approximately 2.3 mcMol/L). The biological half-life of antithrombin is 2 to 3 days. Hereditary antithrombin deficiency, a relatively rare autosomal dominant disorder, produces a thrombotic diathesis (thrombophilia). Individuals with hereditary antithrombin deficiency are usually heterozygous with plasma antithrombin activity results of approximately 40% to 70%. These patients primarily manifest with venous thromboembolism (deep vein thrombosis: DVT and pulmonary embolism: PE) with the potential of development as early as adolescence or younger adulthood. More than 100 different mutations have been identified throughout the gene producing either the more common type I defects (low antithrombin activity and antigen) or the rarer type II defects (dysfunctional protein with low activity and normal antigen). Homozygous antithrombin deficiency appears to be incompatible with life. The incidence of hereditary antithrombin deficiency is approximately 1:2,000 to 1:3,000 in general populations, although minor deficiency (antithrombin activity = 70%-75%) may be more frequent (approximately 1:350-650). In populations with venous thrombophilia, approximately 1% to 2% have antithrombin deficiency. Among the recognized hereditary thrombophilic disorders (including deficiencies of proteins C and S, as well as activated protein C: APC-resistance [factor V Leiden mutation]), antithrombin deficiency may have the highest phenotypic penetrance (greater risk of venous thromboembolism). Arterial thrombosis (eg, stroke, myocardial infarction) has occasionally been reported in association with hereditary antithrombin deficiency.

Useful For: Diagnosis of antithrombin deficiency, acquired or congenital Monitoring treatment of antithrombin deficiency disorders, including infusion of antithrombin therapeutic concentrate

Interpretation: Antithrombin deficiencies due to inherited causes are much less common than those due to acquired causes (see Clinical Information). Diagnosis or hereditary deficiency requires clinical correlation, with the prospect of repeat testing (including antithrombin antigen assay) and family studies (with appropriate counseling). DNA-based diagnostic testing may be helpful, but is not readily available. The clinical significance (thrombotic risk) of antithrombin deficiency in these disorders is not well defined, although antithrombin replacement in severe disseminated intravascular coagulation/ intravascular coagulation and fibrinolysis (DIC/IFC) is being evaluated. Assay of antithrombin activity may be of diagnostic or prognostic value in some acquired deficiency states.
pathophysiology, such as "acute-phase" elevation of coagulation factor VIII or plasma heparin-binding proteins. Increased antithrombin activity is of unknown hemostatic significance. Direct factor Xa inhibitors, rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa) may falsely elevate the antithrombin activity and mask a diagnosis of antithrombin deficiency.

**Reference Values:**

> or =6 months-adults: 80-130%

Normal, full-term newborn infants may have decreased levels (> or =35-40%), which reach adult levels by 90 days postnatal.*

Healthy, premature infants (30-36 weeks gestation) may have decreased levels which reach adult levels by 180 days postnatal.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

**Clinical References:**


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**ATTI 9031**

**Antithrombin Antigen, Plasma**

**Clinical Information:** Antithrombin is a member of the serine protease inhibitor (serpin) superfamily. It is the principal plasma anticoagulant serpin mediating inactivation of serine protease procoagulant enzymes, chiefly thrombin and coagulation factors Xa and IXa.(1) Heparin and certain other naturally occurring glycosaminoglycans markedly enhance antithrombin's anticoagulant activity (approximately 1,000-fold) by providing a template to catalyze formation of covalently bonded, inactive complexes of serine protease and antithrombin that are subsequently cleared from circulation. Antithrombin is the mediator of heparin's anticoagulant activity. The antithrombin gene on chromosome 1 encodes a glycoprotein of approximately 58,000 molecular weight that is synthesized in the liver and is present in a relatively high plasma concentration (approximately 2.3 mcml/L). The biological half-life of antithrombin is 2 to 3 days. Hereditary antithrombin deficiency, a relatively rare, autosomal dominant disorder, produces a thrombotic diathesis (thrombophilia). Individuals with hereditary antithrombin deficiency are usually heterozygous with plasma antithrombin activity results of approximately 40% to 70%. These patients primarily manifest with venous thromboembolism (deep vein thrombosis and pulmonary embolism), with the potential of development as early as adolescence or younger adulthood. More than 100 different mutations have been identified throughout the gene, producing either the more common type I defects (low antithrombin activity and antigen) or the rarer type II defects (dysfunctional protein with low activity and normal antigen).(2) Homozygous antithrombin deficiency appears to be incompatible with life. The incidence of hereditary antithrombin deficiency is approximately 1:2,000 to 1:3,000 in general populations, although minor deficiency (antithrombin activity =70% to 75%) may be more frequent (approximately 1:350 to 1:650). In populations with venous thrombophilia, approximately 1% to 2% have antithrombin deficiency. Among the recognized hereditary thrombophilic disorders (including deficiencies of proteins C and S, as well as activated protein C: APC-resistance [factor V Leiden mutation]), antithrombin deficiency may have the highest phenotypic penetrance (greater risk of venous thromboembolism). Arterial thrombosis (eg, stroke, myocardial infarction) has occasionally been reported in association with hereditary antithrombin deficiency. Hereditary deficiency of antithrombin activity can also occur because of defective glycosylation of this protein in individuals with carbohydrate-deficient glycoprotein syndromes (CDGS).(3) Antithrombin activity assessment may be useful as an adjunct in the diagnosis and management of CDGS. Acquired deficiency of antithrombin is much more common than hereditary deficiency. Acquired deficiency can occur due to: -Heparin therapy (catalysis of antithrombin consumption) -Intravascular coagulation and fibrinolysis (ICF) or disseminated intravascular coagulation (DIC), and other consumptive coagulopathies -Liver disease (decreased synthesis and/or
increased consumption) -Nephrotic syndrome (urinary protein loss) -L-asparaginase chemotherapy (decreased synthesis) -Other conditions

(1) In general, the clinical implications (thrombotic risk) of antithrombin deficiency in these disorders are not well defined, although antithrombin replacement in severe DIC/IFC is being evaluated. (4) Assay of antithrombin activity may be of diagnostic or prognostic value in some acquired deficiency states.

**Useful For:** Assessing abnormal results of the antithrombin activity assay (ATTF / Antithrombin Activity, Plasma), which is recommended as the primary (screening) antithrombin assay. Diagnosing antithrombin deficiency, acquired or congenital, in conjunction with measurement of antithrombin activity. As an adjunct in the diagnosis and management of carbohydrate-deficient glycoprotein syndromes.

**Interpretation:** Hereditary antithrombin deficiency is much less common than acquired deficiency. Diagnosis of hereditary deficiency requires clinical correlation, testing of both antithrombin activity and antithrombin antigen, and may be aided by repeated testing and by family studies. DNA-based diagnostic testing may be helpful, but is generally not readily available. Acquired antithrombin deficiency may occur in association with a number of conditions (see Clinical Information). The clinical significance (thrombotic risk) of acquired antithrombin deficiency is not well established, but accumulating information suggests possible benefit of antithrombin replacement therapy in carefully selected situations. (4) Increased antithrombin activity has no definite clinical significance.

**Reference Values:**

- **Adults:** 80-120%
  - Normal, full-term newborn infants may have decreased levels (> or =35-40%) which reach adult levels by 180 days postnatal. *
  - Healthy, premature infants (30-36 weeks gestation) may have decreased levels which reach adult levels by 180 days postnatal. *

* See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

**Clinical References:**


**APCZ**

**APC Gene, Full Gene Analysis**

**Clinical Information:** Familial adenomatous polyposis (FAP) is an autosomal dominant condition caused by mutations in the APC gene located on the long arm of chromosome 5 (5q21). Classic FAP is characterized by progressive development of hundreds to thousands of adenomatous colon polyps. Polyps may develop during the first decade of life and the majority of untreated FAP patients will develop colon cancer by age 40. Typically, there is a predominance of polyps on the left side of the colon, however, other areas of the colon may also be affected. The presence of extracolonic manifestations is variable and includes gastric and duodenal polyps, ampullary polyps, osteomas, dental abnormalities (unerupted teeth), congenital hypertrophy of the retinal pigment epithelium (CHRPE), benign cutaneous lesions, desmoids tumors, hepatoblastoma, and extracolonic cancers. Common constellations of colonic and extracolonic manifestations have resulted in the designation of 3 clinical variants: Gardner syndrome, Turcot syndrome, and hereditary desmoid disease. Gardner syndrome is characterized by colonic polyps of classic FAP with epidermoid skin cysts and benign osteoid tumors of the mandible and long bones. Turcot syndrome is characterized by multiple colonic polyps and central nervous system (CNS) tumors. Turcot syndrome is an unusual clinical variant of FAP, as it is also considered a clinical variant of hereditary nonpolyposis colorectal cancer (HNPCC). Individuals with Turcot syndrome have CNS tumors in addition to adenomatous polyps. The types of CNS tumor observed helps to distinguish Turcot-FAP variant patients from Turcot-HNPCC variant patients. The predominant CNS tumor associated with the Turcot-FAP variant is medulloblastoma, while glioblastoma is the predominant CNS tumor associated
with Turcot-HNPCC. Hereditary desmoid disease (HDD) is a variant of FAP with multiple desmoids tumors as the predominant feature. Many patients with HDD may not even show colonic manifestations of FAP. APC germline testing may assist clinicians in distinguishing a sporadic desmoid tumor from that associated with FAP. Attenuated FAP (AFAP) is characterized by later onset of disease and a milder phenotype (typically ≤100 adenomatous polyps and fewer extracolonic manifestations) than classic FAP. Typically individuals with AFAP develop symptoms of the disease at least 10 to 20 years later than classically affected individuals. Individuals with AFAP often lack a family history of colon cancer and/or multiple adenomatous polyps. Of note, clinical overlap is observed between AFAP and MYH-associated polyposis (MAP), an autosomal recessive polyposis syndrome typically associated with fewer than 100 polyps. Although the clinical phenotype of MAP remains somewhat undefined, extracolonic manifestations, including CHRPE have been described in affected patients. Given the phenotypic overlap of AFAP and MAP, these tests are commonly ordered together or in a reflex fashion. See Colonic Polyposis Syndromes Testing Algorithm in Special Instructions for additional information. Also see Hereditary Colorectal Cancer: Adenomatous Polyposis Syndromes (September 2004 Communique) in publications for additional information.

**Useful For:** Confirmation of familial adenomatous polyposis (FAP) diagnosis for patients with clinical features

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Apolipoprotein A-I (APOA1) Gene, Full Gene Analysis**

**Clinical Information:** The systemic amyloidoses are a number of disorders of varying etiology characterized by extracellular protein deposition. The most common form is an acquired amyloidosis secondary to multiple myeloma or monoclonal gammopathy of unknown significance (MGUS) in which the amyloid is composed of immunoglobulin light chains. In addition to light chain amyloidosis, there are a number of acquired amyloidoses caused by the misfolding and precipitation of a wide variety of proteins. There are also hereditary forms of amyloidosis. The hereditary amyloidoses comprise a group of autosomal dominant, late-onset diseases that show variable penetrance. A number of genes have been associated with hereditary forms of amyloidosis including those that encode transthyretin, apolipoprotein A-I, apolipoprotein A-II, fibrinogen alpha chain, gelsolin, cystatin C, and lysozyme. Apolipoprotein A-I, apolipoprotein A-II, lysozyme, and fibrinogen alpha-chain amyloidosis present as non-neuropathic systemic amyloidosis, with renal dysfunction being the most prevalent manifestation. Apolipoprotein A-I amyloidosis is also associated with additional organ system involvement, including clinical manifestations in the liver, heart, skin, and larynx. In addition, the G26R APOA1 mutation has been associated with a neuropathic presentation. To date, at least 16 amyloidogenic mutations have been identified within the APOA1 gene. The majority of these are missense mutations, although deletion/insertion mutations have also been described. There is some evidence of genotype-phenotype correlations. Mutations that occur near the amino terminal portion of the protein are more often associated with hepatic and renal amyloidosis, while mutations occurring near the carboxyl terminal portion of the gene are more often associated with cardiac, cutaneous, and laryngeal amyloidosis. The majority of mutations reported to date occur at 1 of 2 hot spots spanning amino acid residues 50 through 93 and 170 through 178. Mutations in the APOA1 gene have also been linked to familial...
hypoalphalipoproteinemia. Patients carrying 1 APOA1 mutation typically demonstrate reduced levels of high-density lipoprotein (HDL) cholesterol, which is associated with increased risk for coronary artery disease. Comparatively, the presence of 2 APOA1 mutations generally results in complete absence of HDL cholesterol and may include additional clinical features such as xanthomas or corneal opacities. Due to the clinical overlap between the acquired and hereditary forms, it is imperative to determine the specific type of amyloidosis in order to provide an accurate prognosis and consider appropriate therapeutic interventions. Tissue-based, laser capture tandem mass spectrometry might serve as a useful test preceding gene sequencing to better characterize the etiology of the amyloidosis, particularly in cases that are not clear clinically.

**Useful For:** Diagnosis of individuals suspected of having apolipoprotein A-I (APOA1) gene-associated familial amyloidosis

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Apolipoprotein A-II (APOA2) Gene, Full Gene Analysis**

**Clinical Information:** The systemic amyloidoses are a number of disorders of varying etiology characterized by extracellular protein deposition. The most common form is an acquired amyloidosis secondary to multiple myeloma or monoclonal gammopathy of unknown significance (MGUS) in which the amyloid is composed of immunoglobulin light chains. In addition to light chain amyloidosis, there are a number of acquired amyloidoses caused by the misfolding and precipitation of a wide variety of proteins. There are also hereditary forms of amyloidosis. The hereditary amyloidoses comprise a group of autosomal dominant, late-onset diseases that show variable penetrance. A number of genes have been associated with hereditary forms of amyloidosis, including those that encode transthyretin, apolipoprotein A-I, apolipoprotein A-II, fibrinogen alpha chain, gelosin, cystatin C, and lysozyme. Apolipoprotein A-I, apolipoprotein A-II, lysozyme, and fibrinogen alpha chain amyloidosis present as non-neuropathic systemic amyloidosis, with renal dysfunction being the most prevalent manifestation. Apolipoprotein A-II amyloidosis typically presents as a very slowly progressive disease. Age of onset is highly variable, ranging from adolescence to the fifth decade. To date, all mutations that have been identified within the APOA2 gene occur within the stop codon and result in a 21-residue C-terminal extension of the apolipoprotein A-II protein. Due to the clinical overlap between the acquired and hereditary forms, it is imperative to determine the specific type of amyloidosis in order to provide an accurate prognosis and consider appropriate therapeutic interventions. Tissue-based, laser capture tandem mass spectrometry might serve as a useful test preceding gene sequencing to better characterize the etiology of the amyloidosis, particularly in cases that are not clear clinically.

**Useful For:** Diagnosis of individuals suspected of having apolipoprotein A-II-associated familial amyloidosis

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.
pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.


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**APABR**

**Apolipoprotein A1 and B, Plasma**

**Clinical Information:** Apolipoprotein B (ApoB) is the primary protein component of low-density lipoprotein (LDL). Apolipoprotein A1 (ApoA1) is the primary protein associated with high-density lipoprotein (HDL). Both ApoB and ApoA1 are more strongly associated with cardiovascular disease than the corresponding lipoprotein cholesterol fraction (see APLA1 / Apolipoprotein A1, Plasma and APLB / Apolipoprotein B, Plasma). However, the most powerful risk prediction value of these proteins appears to be in their ratio (ie, ApoB:ApoA1). ApoB is present in all atherogenic lipoproteins including LDL, Lp(a), intermediate-density lipoprotein (IDL), and very low-density lipoprotein (VLDL) remnants. ApoA1 is the nucleating protein around which HDL forms during reverse cholesterol transport. Therefore, the ApoB:ApoA1 ratio represents the balance between atherogenic and antitherogenic lipoproteins. Several large prospective studies have shown that the ApoB:ApoA1 ratio performs as well, and often better, than traditional lipids as an indicator of risk.(1-3)

**Useful For:** Assessment of residual risk in patients at target non-HDL-C (or LDL-C) Follow-up studies in individuals with non-HDL-C (or LDL-C) values inconsistent with risk factors or clinical presentation Definitive studies of cardiac risk factors in individuals with significant family histories of coronary artery disease or other increased risk factors

**Interpretation:** An elevated apolipoprotein B (ApoB) level confers increased risk of coronary artery disease and can be used as a therapeutic target analogous to non-HDL-C and LDL-C. Risk Category Therapeutic Target: ApoB Non-HDL-C LDL-C Moderate to High <90 mg/dL <130 mg/dL <100 mg/dL Very High <80 mg/dL <100 mg/dL <70 mg/dL Extremely low values of ApoB (<48 mg/dL) are related to malabsorption of food lipids and can lead to polyneuropathy. A reduced apolipoprotein A1 (ApoA1) level confers an increased risk of coronary artery disease. Identification of an ApoA1 <25 mg/dL may be helpful in the detection of a genetic disorder such as Tangier disease. An elevated ApoB:ApoA1 ratio confers an increased risk of coronary artery disease.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Apolipoprotein A (mg/dL)</th>
<th>Apolipoprotein B (mg/dL)</th>
<th>Apolipoprotein B/A1 ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not established</td>
<td>Not established</td>
<td>Not established</td>
<td></td>
</tr>
<tr>
<td>2-17 years</td>
<td>Low: low: 115-120 Acceptable: Acceptable: high: 90-109 High: &gt;120</td>
<td>&gt; or =110</td>
<td></td>
</tr>
<tr>
<td>&gt;18 years</td>
<td>&gt; or =120</td>
<td>Desirable: Desirable: 90-99 Borderline high: 100-119 High: 120-139 Very high: &gt; or =140</td>
<td>Lower Risk: Risk: 0.7-0.9 Higher Risk: &gt;0.9 Females</td>
</tr>
</tbody>
</table>

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APABR 37920

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Apolipoprotein A1, Plasma

Clinical Information: Apolipoprotein A1 (ApoA1) is the primary protein associated with high-density lipoprotein (HDL) particles, and plays a central role in reverse cholesterol transport. (1) HDL cholesterol (HDL-C) and ApoA1 concentrations are inversely related to the risk for coronary artery disease (CAD). (2) There are a variable number of ApoA1 proteins per HDL particle. Therefore, ApoA1 is not a 1:1 surrogate marker for HDL particles. Similarly, the number of ApoA1 proteins and the amount of cholesterol contained in HDL particles is highly variable. This heterogeneity has led to unique clinical findings related to ApoA1 compared with HDL-C. Increased ApoA1 concentrations are more strongly associated with a reduction in risk of a first myocardial infarction than HDL-C concentrations. (3) Low concentrations of ApoA1, but not HDL-C, are predictive of preclinical atherosclerosis as assed by computed tomography estimated coronary artery calcium (CAC) scoring. (4) Increased ApoA1, but not HDL-C concentrations, are associated with reduced cardiovascular events among statin-treated patients, even when LDL-C <50 mg/dL. (5) In statin-treated patients, patients whose ApoA1 increased while on treatment were at lower risk than those whose ApoA1 did not increase.

Useful For: Evaluation of risk for atherosclerotic cardiovascular disease Helpful to aid in the detection of Tangier disease

Interpretation: Low levels of apolipoprotein A1 (ApoA1) confer increased risk of atherosclerotic cardiovascular disease. ApoA1 <25 mg/dL may aid in the detection of a genetic disorder such as Tangier disease.

Reference Values:

<table>
<thead>
<tr>
<th>Age</th>
<th>Apolipoprotein A (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not established</td>
<td></td>
</tr>
<tr>
<td>2-17 years</td>
<td>Low: low: 115-120 Acceptable: &gt;120</td>
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<tr>
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<td>&gt; or =120 Females</td>
</tr>
<tr>
<td>Age</td>
<td>Apolipoprotein A (mg/dL)</td>
</tr>
<tr>
<td>Not established</td>
<td></td>
</tr>
<tr>
<td>2-17 years</td>
<td>Low: low: 115-120 Acceptable: &gt;120</td>
</tr>
<tr>
<td>&gt;18 years</td>
<td>&gt; or =140</td>
</tr>
</tbody>
</table>

Apolipoprotein B, Plasma

Clinical Information: Apolipoprotein B (ApoB) is the primary protein component of low-density lipoprotein (LDL). LDL contains a variable amount of cholesterol, but each LDL contains exactly 1 ApoB protein. Therefore, ApoB is a superior indicator of circulating LDL compared to LDL cholesterol (LDL-C). ApoB has been demonstrated to perform equally with LDL particles measured by nuclear magnetic resonance spectroscopy.(1) ApoB is strongly associated with increased risk of developing cardiovascular disease (CVD) and often outperforms LDL-C at predicting risk of coronary heart disease.(2-4) Patients with acceptable non-HDL-C (or LDL-C) but elevated ApoB remain at higher risk of developing CVD; conversely, patients with acceptably low ApoB but moderate non-HDL-C or LDL-C elevations are at a reduced risk for CVD.(5,6) Finally, in 7 different placebo-controlled randomized clinical trials, on-statin reduction of ApoB was more closely related to CVD risk reduction than non-HDL-C or LDL-C.(7)

Useful For: Assessment of residual risk in patients at target non high-density lipoprotein-cholesterol (HDL-C) (or low-density lipoprotein-cholesterol: LDL-C) Follow-up studies in individuals with non-HDL-C (or LDL-C) values inconsistent with risk factors or clinical presentation Definitive studies of cardiac risk factors in individuals with significant family histories of coronary artery disease or other increased risk factors Confirmation of suspected abetalipoproteinemia or hypobetalipoproteinemia

Interpretation: Elevated ApoB confers increased risk of coronary artery disease ApoB can be used as a therapeutic target analogous to non-HDL-C and LDL-C. Risk Category Therapeutic Target: ApoB Non-HDL-C LDL-C Moderate to High <90 mg/dL <130 mg/dL <100 mg/dL Very High <80 mg/dL <100 mg/dL <70 mg/dL Extremely low values of ApoB (<48 mg/dL) are related to malabsorption of food lipids and can lead to polyneuropathy.

Reference Values:

<table>
<thead>
<tr>
<th>Age</th>
<th>Apolipoprotein B (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not established</td>
<td></td>
</tr>
<tr>
<td>2-17 years</td>
<td>Acceptable: high: 90-109 High: &gt; 110</td>
</tr>
<tr>
<td>&gt;18 years</td>
<td>Desirable: Desirable: 90-99 Borderline high: 100-119 High: 120-139 Very high: &gt; 140</td>
</tr>
</tbody>
</table>


**APOE**

**Clinical Information:** Apolipoproteins are structural constituents of lipoprotein particles that participate in lipoprotein synthesis, secretion, processing, and metabolism. Apolipoproteins have critical roles in blood lipid metabolism. Defects in apolipoprotein E (Apo E) are responsible for familial dysbetalipoproteinemia, or type III hyperlipoproteinemia, in which increased plasma cholesterol and triglycerides result from impaired clearance of chylomicron and very-low-density lipoprotein (VLDL) remnants. The human APOE gene is located on chromosome 19. The 3 common APOE alleles are designated e2, e3, and e4, which encode the Apo E isoforms E2, E3, and E4, respectively. E3, the most common isoform in Caucasians, shows cysteine (Cys) at amino acid position 112 and arginine (Arg) at position 158. E2 and E4 differ from E3 by single amino acid substitutions at positions 158 and 112, respectively (E2: Arg158->Cys; E4: Cys112->Arg). The allele frequencies for most Caucasian populations are as follows: -e2=8% to 12% -e3=74% to 78% -e4=14% to 15% E2 and E4 are both associated with higher plasma triglyceride concentrations. Over 90% of individuals with type III hyperlipoproteinemia are homozygous for the e2 allele. However, <10% of individuals homozygous for the e2 allele have overt type III hyperlipoproteinemia. This suggests that other genetic, hormonal, or environmental factors must contribute to the phenotypic expression of the disease. The e4 allele has been linked to pure elevations of low-density lipoproteins (LDL). Patients with a lipid profile consistent with type III hyperlipidemia are candidates for analysis of their APOE genotype. The APOE gene is also a known susceptibility gene for Alzheimer disease. The e4 allele is associated with an increased risk for Alzheimer disease, particularly late-onset disease, in a dose-dependent manner. This risk is also influenced by other factors. It is estimated that individuals with the APOE e3/e4 genotype have a 4-fold relative risk for Alzheimer disease, while homozygotes for e4 allele have a 12-fold relative risk. Several studies have suggested a protective effect of the APOE e2 allele. The APOE e4 allele, however, is neither sufficient nor necessary for the development of Alzheimer disease. Approximately 50% of individuals with Alzheimer disease carry an e4 allele and many individuals who have an e4 allele will never develop Alzheimer disease. The use of APOE analysis for predictive testing for Alzheimer disease is not currently recommended by the American College of Medical Genetics due to limited clinical utility and poor predictive value.

**Useful For:** Determining the specific apolipoprotein E (APOE) genotypes in patients with type III hyperlipoproteinemia APOE genotyping has been used to assess susceptibility for Alzheimer disease. However, the use of APOE analysis for predictive testing for Alzheimer disease is not currently recommended by the American College of Medical Genetics due to limited clinical utility and poor predictive value.

**Interpretation:** An interpretive report will be provided.


**FAPLG 57629**

**Apple IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**APPL 82712**

**Apple, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

Class IgE kU/L Interpretation

0 Negative

**Apricot, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**Clinical Information:** The activated partial thromboplastin time (APTT) mix is only performed when the APTT is abnormally prolonged. Please refer to test APTTB / Activated Partial Thromboplastin Time (APTT), Plasma for interpretation of results. The APTT mixing test is used to evaluate a prolonged APTT test result, especially when mixing test results are combined with results of other coagulation tests and clinical information, to assist in differentiating coagulation factor deficiencies from coagulation inhibitors.

**Useful For:** Screening for certain coagulation factor deficiencies and abnormalities (eg, factor VIII, IX, XI, or XII). Detection of coagulation inhibitors such as lupus anticoagulant, antiphospholipid antibodies, specific factor inhibitors, and nonspecific inhibitors.

**Interpretation:** Prolongation of the activated partial thromboplastin time (APTT) can occur as a result of deficiency of 1 or more coagulation factors (acquired or congenital in origin), or the presence of an inhibitor of coagulation such as heparin, a lupus anticoagulant, a "nonspecific" inhibitor such as a monoclonal immunoglobulin, or a specific coagulation factor inhibitor. The APTT mixing study, using equal volumes of patient and normal pool plasma, may be performed on specimens with a prolonged APTT to assist in differentiating coagulation factor deficiencies from coagulation inhibitors of all types (1-4). Correction of the APTT mix to within the normal reference range usually indicates a coagulation factor deficiency (normal plasma in the mixture ensures at least 50% activity of all coagulation factors). If the prolonged APTT is due to an inhibitor (eg, specific coagulation factor inhibitor, lupus anticoagulant, heparin), the APTT mix typically fails to correct a prolonged APTT. However, the presence of a weak inhibitor may be missed by the APTT mixing study. Accurate interpretation of both APTT and APTT mixing study results may often require additional testing. For example, the thrombin time (TT) test is helpful for identifying or excluding the presence of heparin, the platelet neutralization procedure (PNP, using a modified APTT method) for identifying or excluding lupus anticoagulant, the prothrombin time (PT) and dilute Russell’s viper venom time (DRVVT) for further assessment of the common procoagulant pathway, and coagulation factor assays to detect and identify deficient or abnormal factors. These assays are available as components of reflexive and interpretive testing panels in the Special Coagulation Laboratory (eg, PROCT / Prolonged Clot Time Profile). Shortening of the APTT usually reflects either elevation of factor VIII activity secondary to acute or chronic illness or inflammation, or spurious results from suboptimal venipuncture, specimen collection or processing. A normal or shortened APTT result does not exclude a hemostatic defect; and specific clotting factor assays should be performed despite a normal APTT when there is clinical impression of bleeding diathesis.

**Reference Values:**
Only orderable as part of a coagulation consultation. For more information see 1 of the following:
- LUPPR / Lupus Anticoagulant Profile
- BDIAL / Bleeding Diathesis Profile
- THRMP / Thrombophilia Profile
- PROCT / Prolonged Clot Time Profile

An interpretive report will be provided.

Clinical Information: California (LaCrosse) Virus: California (LaCrosse) virus is a member of the Bunyaviridae family and is one of the arthropod-borne encephalitides. It is transmitted by various Aedes and Culex mosquitoes and is found in such intermediate hosts as the rabbit, squirrel, chipmunk, and field mouse. California meningoencephalitis is usually mild and occurs in late summer. Ninety percent of infections are seen in children less than 15 years of age, usually from rural areas. The incubation period is estimated to be 7 days and acute illness lasts 10 days or less in most instances. Typically, the first symptoms are nonspecific, lasting 1 to 3 days, and are followed by the appearance of central nervous system (CNS) signs and symptoms such as stiff neck, lethargy, and seizures, which usually abate within 1 week. Symptomatic infection is almost never recognized in those over 18 years old. The most important sequelae of California virus encephalitis is epilepsy, which occurs in about 10% of children; almost always in patients who have had seizures during the acute illness. A few patients (estimated 2%) have persistent paresis. Learning disabilities or other objective cognitive deficits have been reported in a small proportion (no more than 2%) of patients. Learning performance and behavior of most recovered patients are not distinguishable from comparison groups in these same areas. Eastern Equine Encephalitis (EEE): EEE is within the alphavirus group. It is a low prevalence cause of human disease in the eastern and Gulf Coast states. EEE is maintained by a cycle of mosquito/wild bird transmission, peaking in the summer and early fall, when man may become an adventitious host. The most common clinically apparent manifestation is a mild undifferentiated febrile illness, usually with headache. CNS involvement is demonstrated in only a minority of infected individuals, it is more abrupt and more severe than with other arboviruses, with children being more susceptible to severe disease. Fatality rates are approximately 70%. St. Louis Encephalitis (SLE): Areas of outbreaks of SLE since 1933 have involved the western United States, Texas, the Ohio-Mississippi Valley, and Florida. The vector of transmission is the mosquito. Peak incidence occurs in summer and early autumn. Disease onset is characterized by generalized malaise, fever, chills, headache, drowsiness, nausea, and sore throat or cough, followed in 1 to 4 days by meningeal and neurologic signs. The severity of illness increases with advancing age; persons over 60 years have the highest frequency of encephalitis. Symptoms of irritability, sleeplessness, depression, memory loss, and headaches can last up to 3 years. Western Equine Encephalitis (WEE): The virus that causes WEE is widely distributed throughout the United States and Canada; disease occurs almost exclusively in the western states and Canadian provinces. The relative absence of the disease in the eastern United States probably reflects a paucity of the vector mosquito species, Culex tarsalis, and possibly a lower pathogenicity of local virus strains. The disease usually begins suddenly with malaise, fever, and headache, often with nausea and vomiting. Vertigo, photophobia, sore throat, respiratory symptoms, abdominal pain, and myalgia are also common. Over a few days, the headache intensifies; drowsiness and restlessness may merge into a coma in severe cases. In infants and children, the onset may be more abrupt than for adults. WEE should be suspected in any case of febrile CNS disease from an endemic area. Infants are highly susceptible to CNS disease and about 20% of cases are under 1 year of age. There is an excess of males with WEE clinical encephalitis, averaging about twice the number of infections detected in females. After recovery from the acute disease, patients may require from several months to 2 years to overcome the fatigue, headache, and irritability. Infants and children are at higher risk of permanent brain damage after recovery than adults.

Useful For: Aiding the diagnosis of arboviral encephalitis (California [LaCrosse], St. Louis, Eastern equine and Western equine encephalitis)

Interpretation: In patients infected with these or related viruses, IgM class antibody is reliably detected within 1 to 3 weeks of onset, peaking and rapidly declining within 3 months. Results from a single serum specimen can differentiate early (acute) infection from past infection with immunity if IgM is positive (suggests acute infection). IgG antibody is generally detectable within 1 to 3 weeks of onset, peaking within 1 to 2 months, and declining slowly thereafter. A single serum specimen IgG of 1:10 or greater indicates exposure to the virus. A 4-fold or greater rise in IgG antibody titer in acute and convalescent sera indicates recent infection. In the United States, it is unusual for any patient to show positive reactions to more than 1 of the arboviral antigens, although Western equine encephalitis and Eastern equine encephalitis antigens will show a noticeable cross-reactivity.

Reference Values:
CALIFORNIA VIRUS (La CROSSE) ENCEPHALITIS ANTIBODY
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

EASTERN EQUINE ENCEPHALITIS ANTIBODY
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

ST. LOUIS ENCEPHALITIS ANTIBODY
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

WESTERN EQUINE ENCEPHALITIS
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

Clinical References:

Arbovirus Antibody Panel, IgG and IgM, Spinal Fluid

Clinical Information: California (LaCrosse) Virus: California (LaCrosse) virus is a member of the Bunyaviridae family and it is one of the arthropod-borne encephalitides. It is transmitted by various Aedes and Culex mosquitoes and is found in such intermediate hosts as the rabbit, squirrel, chipmunk, and field mouse. California meningoencephalitis is usually mild and occurs in late summer. Ninety percent of infections are seen in children younger than 15 years of age, usually from rural areas. The incubation period is estimated to be 7 days and acute illness lasts 10 days or less in most instances. Typically, the first symptoms are nonspecific, lasting 1 to 3 days, and are followed by the appearance of central nervous system (CNS) signs and symptoms such as stiff neck, lethargy, and seizures, which usually abate within 1 week. Symptomatic infection is almost never recognized in those over 18 years old. The most important sequelae of California virus encephalitis is epilepsy, which occurs in about 10% of children; almost always in patients who have had seizures during the acute illness. A few patients (estimated 2%) have persistent paresis. Learning disabilities or other objective cognitive deficits have been reported in a small proportion (2%) of patients. Learning performance and behavior of most recovered patients are not distinguishable from comparison groups in these same areas. Eastern Equine Encephalitis (EEE): EEE is within the alphavirus group. It is a low-prevalence cause of human disease in the eastern and Gulf Coast states. EEE is maintained by a cycle of mosquito/wild bird transmission, peaking in the summer and early fall, when man may become an adventitious host. The most common clinically apparent manifestation is a mild undifferentiated febrile illness, usually with headache. CNS involvement is demonstrated in only a minority of infected individuals, and is more abrupt and more severe than with other arboviruses, with children being more susceptible to severe disease. Fatality rates are approximately 70%. St. Louis Encephalitis (SLE): Areas or outbreaks of SLE since 1933 have involved the western United States, Texas, the Ohio-Mississippi Valley, and Florida. The vector of transmission is the mosquito. Peak incidence occurs in summer and early autumn. Disease onset is characterized by generalized malaise, fever, chills, headache, drowsiness, nausea, and sore throat or cough, followed in 1 to 4 days by meningeal and neurologic signs. The severity of illness increases with advancing age; persons over 60 years have the highest frequency of encephalitis. Symptoms of irritability, sleeplessness, depression, memory loss, and headaches can last up to 3 years.
Western Equine Encephalitis (WEE): The virus that causes WEE is widely distributed throughout the United States and Canada; disease occurs almost exclusively in the western states and Canadian provinces. The relative absence of the disease in the eastern United States probably reflects a paucity of the vector mosquito species, Culex tarsalis, and possibly a lower pathogenicity of local virus strains. The disease usually begins suddenly with malaise, fever, and headache, often with nausea and vomiting. Vertigo, photophobia, sore throat, respiratory symptoms, abdominal pain, and myalgia are also common. Over a few days, the headache intensifies; drowsiness and restlessness may merge into a coma in severe cases. In infants and children, the onset may be more abrupt than for adults. WEE should be suspected in any case of febrile CNS disease from an endemic area. Infants are highly susceptible to CNS disease and about 20% of cases are under 1 year of age. There is an excess of males with WEE clinical encephalitis, averaging about twice the number of infections detected in females. After recovery from the acute disease, patients may require from several months to 2 years to overcome the fatigue, headache, and irritability. Infants and children are at a higher risk of permanent brain damage after recovery than adults.

Useful For: Aiding the diagnosis of arboviral encephalitis (California [LaCrosse], St. Louis, Eastern equine and Western equine encephalitis)

Interpretation: Detection of organism-specific antibodies in the cerebrospinal fluid (CSF) may suggest central nervous system infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of central nervous system infection.

Reference Values:

CALIFORNIA VIRUS (La CROSSE) ENCEPHALITIS ANTIBODY
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

EASTERN EQUINE ENCEPHALITIS ANTIBODY
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

ST. LOUIS ENCEPHALITIS ANTIBODY
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

WESTERN EQUINE ENCEPHALITIS
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

**Useful For:** Identification and differentiation of hepatocellular carcinoma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Arginine Vasopressin, Plasma**

**Clinical Information:** Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), is a hypothalamic polypeptide that is transported along the axons of the synthesizing neurons into the posterior pituitary gland. From there it is released into the systemic circulation after appropriate stimuli. The main regulators of AVP secretion are osmotic stimuli, provided by osmoreceptors located in the anteromedial hypothalamus, and volume stimuli, provided by receptors in neck vessels and heart. Under physiological conditions, volume stimuli always override osmotic stimuli. The absence or presence of AVP is the major physiologic determinant of urinary free water excretion or retention. AVP acts principally on renal collecting tubules to increase water reabsorption. The antidiuretic effects of AVP are mediated by V2 vasopressin receptors. AVP can also increase vascular resistance through stimulation of V1 receptors. Diabetes insipidus (DI) is characterized by the inability to appropriately concentrate urine in response to volume and osmol stimuli. The main causes for DI are decreased AVP production (central DI) or decreased renal response to AVP (nephrogenic DI). AVP can also be secreted inappropriately in certain situations, particularly in elderly patients, leading to water retention and dilutional hyponatremia. Inappropriate AVP secretion might be observed with central nervous system pathology, such as head injury, stroke, or cerebral tumor, or as a side effect of central acting drugs that interfere with the hypothalamic regulation or AVP. Noncentral causes of inappropriate AVP secretion include peripheral stimuli that mimic central vascular hypovolemia, in particular severe low-output cardiac failure, and ectopic AVP secretion (usually by a bronchogenic carcinoma).

**Useful For:** Diagnosis and characterization of diabetes insipidus Diagnosis of psychogenic water intoxication As an adjunct in the diagnosis of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), including ectopic arginine vasopressin production

**Interpretation:** Central diabetes insipidus (DI) can be differentiated from nephrogenic DI by measuring arginine vasopressin (AVP) during a state of maximal, or near maximal, stimulus for AVP release (water deprivation test; perform under medical supervision; stop once plasma osmolality >295 mOsm/kg water or > or =5% loss in body weight) and assessing the antidiuretic response to exogenous administration of the AVP at the conclusion of a water deprivation test: -If AVP is low despite elevated serum osmolality, and the urine osmolality increases significantly after administration of exogenous AVP, the diagnosis is compatible with central DI. -If stimulated AVP is elevated and the administration...
of exogenous AVP results in little or no increase in urine concentration, the patient likely has nephrogenic DI. Mixed forms of DI can exist, and both central and peripheral DI may be incomplete, complicating the interpretation of results. Patients with psychogenic polydipsia will either have a normal response to water deprivation or, in particular in long-standing cases, will show a pattern suggestive of mild nephrogenic DI due to loss of concentrating gradient across the nephron as a result of salt-washout by long-standing polydipsia. An elevated plasma AVP level in a hyponatremic, euvolemic patient might be indicative of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Confirmation of euvolemia is critical in such patients, since an elevated AVP level represents a physiological response to hypovolemia. Seizures, cerebral hemorrhages, cerebral trauma, cerebral tumors, neurosurgery, electroconvulsive therapy, central nervous system acting drugs, and a variety of conditions that reduce apparent blood volume or pressure in central vessels (eg, severe low output cardiac failure) can all result in inappropriate AVP elevations. Depending on the clinical course, these might be short lived. If none of these conditions is present, ectopic AVP secretion, most commonly caused by bronchial carcinoma, should be suspected.

**Reference Values:**

Adults: <4.3 pg/mL

Reference values were determined on platelet-poor EDTA plasma from individuals fasting no longer than overnight.


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**FARI**

57112

**Aripiprazole (Abilify)**

**Reference Values:**

Units: ng/mL

Expected steady state plasma levels in patients receiving recommended daily dosages: 109.0 - 585.0 ng/mL

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**ARVGP**

63160

**Arrhythmogenic Cardiomyopathy Multi-Gene Panel, Blood**

**Clinical Information:** The cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathy can be caused by inherited, genetic factors, or by nongenetic (acquired) causes such as infection or trauma. When the presence or severity of the cardiomyopathy observed in a patient cannot be explained by acquired causes, genetic testing for the inherited forms of cardiomyopathy may be considered. Overall, the cardiomyopathies are some of the most common genetic disorders. The inherited forms of cardiomyopathy include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC or AC), and left ventricular noncompaction (LVNC). Arrhythmogenic right ventricular dysplasia (ARVD or AC), is characterized by breakdown of the myocardium and replacement of the muscle tissue with fibrofatty tissue, resulting in an increased risk of arrhythmia and sudden death. The incidence of ARVC is approximately 1 in 1,000 to 1 in 2,500. Age of onset and severity are variable, but symptoms typically develop in adulthood. ARVC is present in 4% to 22% of athletes with sudden cardiac death, and there is some debate whether high-intensity endurance exercise may cause development of ARVC. ARVC is typically considered a disease of the desmosome, the structure that attaches heart muscle cells to one another. The desmosome provides strength to the muscle tissue and plays a role in signaling between neighboring cells. Variants in the genes associated with ARVC disrupt this function, causing detachment and death of myocardial cells when the heart muscle is under stress. Damaged myocardium is replaced with fat and scar tissue, eventually leading to structural and electrical abnormalities that can lead to arrhythmia. Inheritance of ARVC typically follows an autosomal dominant pattern of inheritance, and variants in DSC2, DSP, and PKP2 account for approximately half of the variants identified in ARVC. However, simultaneous testing of all known ARVC genes is recommended due to the potential for compound heterozygosity (biallelic variants on the same gene) or digenic heterozygosity (variants in 2 different genes). See table for details regarding the genes tested by this panel and associated diseases. Genes included in the Arrhythmogenic
Cardiomyopathy Multi-Gene Panel Gene Protein Inheritance Disease Association

Desmin AD, AR
DCM, ARVC, myofibrillar myopathy, RCM with AV block, neurogenic scapuloperoneal syndrome
Kaeser type, LGMD DSC2 Desmocollin AD, AR ARVC, ARVC + skin and hair findings

DSC2 Desmoglein AD ARVC DSP Desmoiplakin AD, AR ARVC, DCM, Carvajal syndrome JUP Junction
plakoglobin AD, AR ARVC, Naxos disease LMNA Lamin A/C AD, AR DCM, EM, LGMD, congenital muscular dystrophy, ARVC (see OMIM for full listing) PKP2 Plakophilin 2 AD ARVC RYR2 Ryanodine receptor 2 AD ARVC, CPVT, LQTS

DSP Desmoplakin AD ARVC, ARVC, DCM, Carvajal syndrome
JUP Junction plakoglobin AD, AR ARVC, Naxos disease LMNA Lamin A/C AD, AR DCM, EM, LGMD, congenital muscular dystrophy, ARVC (see OMIM for full listing) PKP2 Plakophilin 2 AD ARVC RYR2 Ryanodine receptor 2 AD ARVC, CPVT, LQTS

TMEM43 Transmembrane protein 43 AD ARVC, EMD
TTN Titin AD, AR HCM, DCM, ARVC, myopathy

Abbreviations: Hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), restrictive cardiomyopathy (RCM), limb-girdle muscular dystrophy (LGMD), Emory muscular dystrophy (EMD), catecholaminergic polymorphic ventricular tachycardia (CPVT), long QT syndrome (LQTS), autosomal dominant (AD), autosomal recessive (AR)

Useful For:
Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hereditary arrhythmogenic right ventricular cardiomyopathy (ARVC or AC)
Establishing a diagnosis of ARVC or AC, and in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved
Identifying a pathogenic variant within a gene known to be associated with disease that allows for predictive testing of at-risk family members

Interpretation:
Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values:
An interpretive report will be provided.

Clinical References:

ARSA Gene, Full Gene Analysis

Clinical Information:
Metachromatic leukodystrophy (MLD) is a rare autosomal recessive condition caused by mutations in the arylsulfatase A (ARSA) gene. The incidence of MLD is approximately 1:40,000 to 1:160,000, and the estimated carrier frequency in the general population is 1:100 to 1:200. MLD is characterized by the accumulation of cerebroside sulfate, which causes progressive demyelination and the loss of white matter. There is a variable age of onset. In the early onset form, symptoms appear in the first 1 to 2 years of life and include deterioration of skills such as walking and speaking. In the juvenile form, symptoms can appear between 4 years of age and the age of sexual maturity, and can include a decline in school performance and behavioral problems. Adults can present with a decline in school or job performance, substance abuse, and emotional lability. The diagnosis is suspected in individuals with progressive neurologic dysfunction and molecular resonance imaging evidence of leukodystrophy. The ARSA gene is located on chromosome 22 and has 8 exons. The following 4 mutations, c.459+1G>A, c.1204+1G>A, p.Pro426Leu, and p.Ile179Ser, account for 25% to 50% of mutations in the central and western European populations. The presence of 2 of these mutations within the ARSA gene confirms a diagnosis of metachromatic leukodystrophy. The recommended first-tier tests to screen for MLD are biochemical tests that measure arylsulfatase A enzyme activity in leukocytes and urine: ARSAW / Arylsulfatase A, Leukocytes and ARSU /
Arylsulfatase A, 24 Hour, Urine. Individuals with decreased enzyme activity are more likely to have 2 mutations in the ARSA gene identifiable by molecular gene testing. However, arylsulfatase A enzyme assays cannot distinguish between MLD and ARSA pseudodeficiency, a clinically benign condition that leads to low in vitro ARSA levels, but it is found in 5% to 20% of the normal population. Thus, the diagnosis of MLD must be confirmed by molecular analysis of the ARSA gene.

Useful For: Second-tier test for confirming a diagnosis of metachromatic leukodystrophy (MLD) based on clinical findings and low arylsulfatase A (ARSA) activity levels Carrier testing when there is a family history of MLD, but disease-causing mutations have not been previously identified

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.


Arsenic Fractionation, 24 Hour, Urine

Clinical Information: Arsenic (As) exists in a number of different forms; some are toxic, while others are not. The toxic forms are the inorganic species of As(+3) (As-III), As(+5) (As-V), and their partially detoxified metabolites, monomethylarsine and dimethylarsine. As-III is more toxic than As-V and both are more toxic than mono- and dimethylarsine. The biologic half-life of inorganic arsenic is 4 to 6 hours, while the biologic half-life of the methylated metabolites is 20 to 30 hours. Target organs of As-III-induced effects are the heart, gastrointestinal tract, skin and other epithelial tissues, kidney, and nervous system. Inorganic arsenic is carcinogenic to humans. Symptoms of chronic poisoning, called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can occur. Nontoxic, organic forms of arsenic are present in many foods. Arsenobetaine and arsenocholine are the 2 most common forms of organic arsenic found in food. The most common foods that contain significant concentrations of organic arsenic are shellfish and other predators in the seafood chain (cod, haddock, etc). Some meats such as chicken that have been fed on seafood remnants may also contain the organic forms of arsenic. Following ingestion of arsenobetaine and arsenocholine, these compounds undergo rapid renal clearance to become concentrated in the urine. Organic arsenic is completely excreted within 1 to 2 days after ingestion and there are no residual toxic metabolites. The biologic half-life of organic arsenic is 4 to 6 hours. For reporting purposes, the concentrations of the inorganic forms (As[+3] and As[+5]) along with the methylated forms (monomethylarsine and dimethylarsine) will be summed and reported together as "Inorganic" arsenic. This is consistent with how the biological exposure index (BEI) reference range is reported.

Useful For: Diagnosis of arsenic intoxication in 24-hour urine specimens

Interpretation: The quantitative reference range for fractionated arsenic applies only to the inorganic forms. Concentrations greater than or equal to 20 mcg inorganic arsenic per 24 hours are considered toxic. There is no limit to the normal range for the organic forms of arsenic, since they are not toxic and normally present after consumption of certain food types. For example, a typical finding in a urine specimen with total 24-hour excretion of arsenic of 350 mcg/24 hours would be that more than 95% is
present as the organic species from a dietary source, and less than 5% present as the inorganic species. This would be interpreted as indicating the elevated total arsenic was due to ingestion of the nontoxic form of arsenic, usually found in food. A normal value for blood arsenic does not exclude a finding of an elevated urine inorganic arsenic, due to the very short half-life of blood arsenic.

**Reference Values:**

**TOTAL ARSENIC**

<18 mcg/24 hour

**INORGANIC ARSENIC**

<20 mcg/24 hour

Reference values apply to all ages.

*B* Biological exposure indices (BEI) for arsenic is 35 mcg/L based on the concentration of inorganic arsenic plus methylated metabolites.


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**Arsenic Fractionation, Random, Urine**

**Clinical Information:** Arsenic (As) exists in a number of different forms; some are toxic, while others are not. The toxic forms are the inorganic species of As(+3) (As-III), As(+5) (As-V), and their partially detoxified metabolites, monomethylarsine, and dimethylarsine. As-III is more toxic than As-V and both are more toxic than mono- and dimethylarsine. The biologic half-life of inorganic arsenic is 4 to 6 hours, while the biologic half-life of the methylated metabolites is 20 to 30 hours. Target organs of As-III-induced effects are the heart, gastrointestinal tract, skin and other epithelial tissues, kidney, and nervous system. Inorganic arsenic is carcinogenic to humans. Symptoms of chronic poisoning, called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can occur. Nontoxic, organic forms of arsenic are present in many foods. Arsenobetaine and arsenocholine are the 2 most common forms of organic arsenic found in food. The most common foods that contain significant concentrations of organic arsenic are shellfish and other predators in the seafood chain (cod, haddock, etc). Some meats, such as from chickens that have been fed on seafood remnants, may also contain the organic forms of arsenic. Following ingestion of arsenobetaine and arsenocholine, these compounds undergo rapid renal clearance to become concentrated in the urine. Organic arsenic is completely excreted within 1 to 2 days after ingestion and there are no residual toxic metabolites. The biologic half-life of organic arsenic is 4 to 6 hours. For reporting purposes, the concentrations of the inorganic forms (As[+3] and As[+5]) along with the methylated forms (monomethylarsine and dimethylarsine) will be summed and reported together as 'Inorganic' arsenic. This is consistent with how the biological exposure index (BEI) reference range is reported.

**Useful For:** Diagnosis of arsenic intoxication in random urine specimens

**Interpretation:** The quantitative reference range for fractionated arsenic applies only to the inorganic forms. Concentrations of 20 mcg inorganic arsenic per liter or higher are considered toxic. There is no limit to the normal range for the organic forms of arsenic, since they are not toxic and are normally present after consumption of certain food types. For example, a typical finding in a urine specimen with total 24-hour excretion of arsenic of 350 mcg/24 hours would be that more than 95% is present as the organic species from a dietary source, and less than 5% is present as the inorganic species. This would be interpreted as indicating the elevated total arsenic was due to ingestion of the nontoxic form of arsenic, usually found in food. A normal value for blood arsenic does not exclude a finding of elevated urine inorganic arsenic, due to the very short half-life of blood arsenic.

**Reference Values:**
TOTAL ARSENIC
<20 mcg/L

INORGANIC ARSENIC
<20 mcg/L

Reference values apply to all ages.

*Biological exposure indices (BEI) for arsenic is 35 mcg/L based on the concentration of inorganic arsenic plus methylated metabolites.


**Arsenic Occupational Exposure, Random, Urine**

Clinical Information: Arsenic is perhaps the best known of the metal toxins, having gained notoriety from its extensive use by Renaissance nobility as an antisyphilitic agent and, paradoxically, as an antidote against acute arsenic poisoning. Even today, arsenic is still one of the more common toxicants found in insecticides, and leaching from bedrock to contaminate groundwater. The toxicity of arsenic is due to 3 different mechanisms, 2 of them related to energy transfer. Arsenic covalently and avidly binds to dihydrolipoic acid, a necessary cofactor for pyruvate dehydrogenase. Absence of the cofactor inhibits the conversion of pyruvate to acetyl coenzyme A, the first step in gluconeogenesis. This results in loss of energy supply to anaerobic cells, the predominant mechanism of action of arsenic on neural cells that rely on anaerobic respiration for energy. Neuron cell destruction that occurs after long-term energy loss results in bilateral peripheral neuropathy. Arsenic also competes with phosphate for binding to adenosine triphosphate during its synthesis by mitochondria via oxidative phosphorylation, causing formation of the lower energy adenosine diphosphate monoarsine. This results in loss of energy supply to aerobic cells. Cardiac cells are particularly sensitive to this form of energy loss; fatigue due to poor cardiac output is a common symptom of arsenic exposure. Arsenic furthermore binds avidly with any hydrated sulfhydryl group on protein, distorting the 3-dimensional configuration of that protein, causing it to lose activity. Interaction of arsenic with epithelial cell protein at the sites of highest physiologic concentration, the small intestine and proximal tubule of the kidney, results in cellular degeneration. Epithelial cell erosion in the gastrointestinal tract and proximal tubule are characteristic of arsenic toxicity. Arsenic is also a known carcinogen, but the mechanism of this effect is not definitively known. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can occur. Arsenic exists in a number of different forms; organic forms are nontoxic, inorganic forms are toxic. See ASFRU / Arsenic Fractionation, Random, Urine for details about arsenic forms. Because arsenic is excreted predominantly by glomerular filtration, analysis for arsenic in urine is the best screening test to detect arsenic exposure.

Useful For: Screening test for detection of occupational exposure to arsenic in random urine specimens

Interpretation: Normally, humans consume 5 to 25 mcg of arsenic each day as part of their normal diet; therefore, normal urine arsenic output is less than 35 mcg arsenic per gram creatinine (<35 mcg/g). When exposed to inorganic arsenic, the urine output may be above 1,000 mcg/g and remain elevated for weeks. After a seafood meal (seafood contains a nontoxic, organic form of arsenic), on the other hand, the urine output of arsenic may be above 200 mcg/g, after which it will decline to under 35 mcg/g over a period of 1 to 2 days. Exposure to inorganic arsenic, the toxic form of arsenic, causes prolonged excretion of arsenic in the urine for many days. Urine excretion rates above 1,000 mcg/g indicates significant exposure. The highest value observed at Mayo Clinic was 450,000 mcg/L in a patient with severe symptoms of gastrointestinal distress, shallow breathing with classic "garlic breath," intermittent seizure activity, cardiac arrhythmias, and later onset of peripheral neuropathy.
**Reference Values:**
Only orderable as part of profile. See ARSOR / Arsenic Occupational Exposure with Reflex, Random, Urine or HMSOR / Heavy Metal Occupational Exposure with Reflex, Urine.

**Clinical References:**

**ARSOR 48550**

**Arsenic Occupational Exposure, with Reflex, Random, Urine**

**Clinical Information:** Arsenic is perhaps the best known of the metal toxins, having gained notoriety from its extensive use by Renaissance nobility as an antisyphilitic agent and, paradoxically, as an antidote against acute arsenic poisoning. Even today, arsenic is still one of the more common toxicants found in insecticides, and leaching from bedrock to contaminate groundwater. The toxicity of arsenic is due to 3 different mechanisms, 2 of them related to energy transfer. Arsenic covalently and avidly binds to dihydrolipoic acid, a necessary cofactor for pyruvate dehydrogenase. Absence of the cofactor inhibits the conversion of pyruvate to acetyl coenzyme A, the first step in gluconeogenesis. This results in loss of energy supply to anaerobic cells, the predominant mechanism of action of arsenic on neural cells that rely on anaerobic respiration for energy. Neuron cell destruction that occurs after long-term energy loss results in bilateral peripheral neuropathy. Arsenic also competes with phosphate for binding to adenosine triphosphate during its synthesis by mitochondria via oxidative phosphorylation, causing formation of the lower energy adenosine diphosphate monoarsine. This results in loss of energy supply to aerobic cells. Cardiac cells are particularly sensitive to this form of energy loss; fatigue due to poor cardiac output is a common symptom of arsenic exposure. Arsenic furthermore binds avidly with any hydrated sulfhydryl group on protein, distorting the 3-dimensional configuration of that protein, causing it to lose activity. Interaction of arsenic with epithelial cell protein at the sites of highest physiologic concentration, the small intestine and proximal tubule of the kidney, results in cellular degeneration. Epithelial cell erosion in the gastrointestinal tract and proximal tubule are characteristic of arsenic toxicity. Arsenic is also a known carcinogen, but the mechanism of this effect is not definitively known. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arsieniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can occur. Arsenic exists in a number of different forms; organic forms are nontoxic, inorganic forms are toxic. See ASFRU / Arsenic Fractionation, Random, Urine for details about arsenic forms. Because arsenic is excreted predominantly by glomerular filtration, analysis for arsenic in urine is the best screening test to detect arsenic exposure.

**Useful For:** Preferred screening test for detection of occupational exposure to arsenic in random urine specimens

**Interpretation:** Normally, humans consume 5 to 25 mcg of arsenic each day as part of their normal diet; therefore, normal urine arsenic output is less than 35 mcg arsenic per gram creatinine (<35 mcg/g). When exposed to inorganic arsenic, the urine output may be above 1,000 mcg/g and remain elevated for weeks. After a seafood meal (seafood contains a nontoxic, organic form of arsenic), on the other hand, the urine output of arsenic may be above 200 mcg/g, after which it will decline to under 35 mcg/g over a period of 1 to 2 days. Exposure to inorganic arsenic, the toxic form of arsenic, causes prolonged excretion of arsenic in the urine for many days. Urine excretion rates above 1,000 mcg/g indicates significant exposure. The highest value observed at Mayo Clinic was 450,000 mcg/L in a patient with severe symptoms of gastrointestinal distress, shallow breathing with classic "garlic breath," intermittent seizure activity, cardiac arrhythmias, and later onset of peripheral neuropathy.

**Reference Values:**
Biological Exposure Indices (BEI)
<35 mcg/L at end of work week
Arsenic with Reflex, 24 Hour, Urine

Clinical Information: Arsenic is perhaps the best known of the metal toxins, having gained notoriety from its extensive use by Renaissance nobility as an antisyphilitic agent and, paradoxically, as an antidote against acute arsenic poisoning. Even today, arsenic is still one of the more common toxicants found in insecticides, and leaching from bedrock to contaminate groundwater. The toxicity of arsenic is due to 3 different mechanisms, 2 of them related to energy transfer. Arsenic covalently and avidly binds to dihydrolipoic acid, a necessary cofactor for pyruvate dehydrogenase. Absence of the cofactor inhibits the conversion of pyruvate to acetyl coenzyme A, the first step in gluconeogenesis. This results in loss of energy supply to anaerobic cells, the predominate mechanism of action of arsenic on neural cells that rely on anaerobic respiration for energy. Neuron cell destruction that occurs after long-term energy loss results in bilateral peripheral neuropathy. Arsenic also competes with phosphate for binding to adenosine triphosphate during its synthesis by mitochondria via oxidative phosphorylation, causing formation of the lower energy adenosine diphosphate monoarsine. This results in loss of energy supply to aerobic cells. Cardiac cells are particularly sensitive to this form of energy loss; fatigue due to poor cardiac output is a common symptom of arsenic exposure. Arsenic furthermore binds avidly with any hydrated sulfhydryl group on protein, distorting the 3-dimensional configuration of that protein, causing it to lose activity. Interaction of arsenic with epithelial cell protein at the sites of highest physiologic concentration, the small intestine and proximal tubule of the kidney, results in cellular degeneration. Epithelial cell erosion in the gastrointestinal tract and proximal tubule are characteristic of arsenic toxicity. Arsenic is also a known carcinogen, but the mechanism of this effect is not definitively known. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can occur. Because arsenic is excreted predominantly by glomerular filtration, analysis for arsenic in urine is the best screening test to detect arsenic exposure. Arsenic exists in a number of different forms; organic forms are nontoxic, inorganic forms are toxic. See ASFR / Arsenic Fractionation, 24 Hour, Urine for details about arsenic forms.

Useful For: Preferred screening test for detection of arsenic exposure in 24-hour urine specimens

Interpretation: Normally, humans consume 5 to 25 mcg of arsenic each day as part of their normal diet; therefore, normal urine arsenic output is less than 25 mcg/specimen. After a seafood meal (seafood contains a nontoxic, organic form of arsenic), the urine output of arsenic may increase to 300 mcg/specimen for 1 day, after which it will decline to below 25 mcg/specimen. Exposure to inorganic arsenic, the toxic form of arsenic, causes prolonged excretion of arsenic in the urine for many days. Urine excretion rates above 1,000 mcg/specimen indicate significant exposure. The highest level observed at Mayo Clinic was 450,000 mcg/specimen in a patient with severe symptoms of gastrointestinal distress, shallow breathing with classic "garlic breath," intermittent seizure activity, cardiac arrhythmias, and later onset of peripheral neuropathy.

Reference Values:
0-17 years: not established
> or =18 years: <18 mcg/24 hour

Arsenic, Blood

Clinical Information: Arsenic (As) exists in a number of toxic and nontoxic forms. The toxic forms are the inorganic species As(+5), also denoted as As(V), the more toxic As(+3), also known as As(III), and their partially detoxified metabolites, monomethylarsine (MMA) and dimethylarsine (DMA). Detoxification occurs in the liver as As(+3) is oxidized to As(+5) and then methylated to MMA and DMA. As a result of these detoxification steps, As(+3) and As(+5) are found in the urine shortly after ingestion, whereas MMA and DMA are the species that predominate more than 24 hours after ingestion. Blood concentrations of arsenic are elevated for a short time after exposure, after which arsenic rapidly disappears into tissues because of its affinity for tissue proteins. The body treats arsenic like phosphate, incorporating it wherever phosphate would be incorporated. Arsenic "disappears" into the normal body pool of phosphate and is excreted at the same rate as phosphate (excretion half-life of 12 days). The half-life of inorganic arsenic in blood is 4 to 6 hours, and the half-life of the methylated metabolites is 20 to 30 hours. Abnormal blood arsenic concentrations (>12 ng/mL) indicate significant exposure, but will only be detected immediately after exposure. Arsenic is not likely to be detected in blood specimens drawn more than 2 days after exposure because it has become integrated into nonvascular tissues. Consequently, blood is not a good specimen to screen for arsenic, although periodic blood levels can be determined to follow the effectiveness of therapy. Urine is the preferred specimen for assessment of arsenic exposure. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic (abdominal pain), diarrhea, and paresthesias of the hands and feet can occur.

Useful For: Detection of acute or very recent arsenic exposure Monitoring the effectiveness of therapy

Interpretation: Abnormal blood arsenic concentrations (>12 ng/mL) indicate significant exposure. Absorbed arsenic is rapidly distributed into tissue storage sites with a blood half-life of <6 hours. Unless a blood specimen is drawn within 2 days of exposure, arsenic is not likely to be detected in a blood specimen.

Reference Values: 0-12 ng/mL Reference values apply to all ages.


Arsenic, Hair

Clinical Information: Arsenic circulating in the blood will bind to protein by formation of a covalent complex with sulfhydryl groups of the amino acid cysteine. Keratin, the major structural protein in hair and nails, contains many cysteine residues and, therefore, is one of the major sites for accumulation of arsenic. Since arsenic has a high affinity for keratin, the concentration of arsenic in hair is higher than in other tissues. Arsenic binds to keratin at the time of exposure, "trapping" the arsenic in hair. Therefore, hair analysis for arsenic is not only used to document that an exposure occurred, but when it occurred. Hair collected from the nape of the neck can be used to document recent exposure. Axillary or pubic hair are used to document long-term (6 months-1 year) exposure.

Useful For: Detection of nonacute arsenic exposure in hair specimens

Interpretation: Hair grows at a rate of approximately 0.5 inch/month. Hair keratin synthesized today will protrude through the skin in approximately 1 week. Thus, a hair specimen collected at the skin level represents exposure of 1 week ago, 1 inch distally from the skin represents exposure 2 months ago, etc. Hair arsenic levels above 1.00 mcg/g dry weight indicates excessive exposure. It is normal for some
arsenic to be present in hair, as everybody is exposed to trace amounts of arsenic from the normal diet. The highest hair arsenic observed at Mayo Clinic was 210 mcg/g dry weight in a case of chronic exposure that was the cause of death.

**Reference Values:**
0-15 years: not established
> or =16 years: 0.0-0.9 mcg/g of hair

**Clinical References:**

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**Arsenic, Nails**

**Clinical Information:** Arsenic circulating in the blood will bind to protein by formation of a covalent complex with sulfhydryl groups of the amino acid cysteine. Keratin, the major structural protein in hair and nails, contains many cysteine residues and, therefore, is one of the major sites for accumulation of arsenic. Since arsenic has a high affinity for keratin, the concentration of arsenic in nails is higher than in other tissues. Several weeks after exposure, transverse white striae, called Mees' lines, may appear in the fingernails.

**Useful For:** Detection of nonacute arsenic exposure

**Interpretation:** Nails grow at a rate of approximately 0.1 inch/month. Nail keratin synthesized today will grow to the distal end in approximately 6 months. Thus, a nail specimen collected at the distal end represents exposure of 6 months ago. Nail arsenic above 1.0 mcg/g dry weight indicates excessive exposure. It is normal for some arsenic to be present in nails, as everybody is exposed to trace amounts of arsenic from the normal diet. The highest hair or nail arsenic observed at Mayo Clinic was 210 mcg/g dry weight in a case of chronic exposure that was the cause of death.

**Reference Values:**
0-15 years: not established
> or =16 years: 0.0-0.9 mcg/g of nails


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**Arsenic/Creatinine Ratio, Urine**

**Clinical Information:** Arsenic is perhaps the best known of the metal toxins, having gained notoriety from its extensive use by Renaissance nobility as an antisyphilitic agent and, paradoxically, as an antidote against acute arsenic poisoning. Even today, arsenic is still one of the more common toxicants found in insecticides, and leaching from bedrock to contaminate groundwater. The toxicity of arsenic is due to 3 different mechanisms, 2 of them related to energy transfer. Arsenic covalently and avidly binds to dihydrolipoic acid, a necessary cofactor for pyruvate dehydrogenase. Absence of the cofactor inhibits the conversion of pyruvate to acetyl coenzyme A, the first step in gluconeogenesis. This results in loss of energy supply to anaerobic cells, the predominant mechanism of action of arsenic on neural cells that rely on anaerobic respiration for energy. Neuron cell destruction that occurs after long-term energy loss results in bilateral peripheral neuropathy. Arsenic also competes with phosphate for binding to adenosine triphosphate during its synthesis by mitochondria via oxidative phosphorylation, causing formation of the lower energy adenosine diphosphate monoarsine. This results in loss of energy supply to aerobic cells. Cardiac cells are particularly sensitive to this form of energy loss; fatigue due to poor cardiac output is a common symptom of arsenic exposure. Arsenic furthermore binds avidly with any hydrated sulfhydryl group on protein, distorting the 3-dimensional configuration of that protein, causing it to lose activity. Interaction of arsenic with epithelial cell protein at the sites of highest physiologic concentration, the
small intestine and proximal tubule of the kidney, results in cellular degeneration. Epithelial cell erosion in the gastrointestinal tract and proximal tubule are characteristic of arsenic toxicity. Arsenic is also a known carcinogen, but the mechanism of this effect is not definitively known. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can occur. Arsenic exists in a number of different forms; organic forms are nontoxic, inorganic forms are toxic. See ASFRU / Arsenic Fractionation, Random, Urine for details about arsenic forms. Because arsenic is excreted predominantly by glomerular filtration, analysis for arsenic in urine is the best screening test to detect arsenic exposure.

**Useful For:** Screening test for detection of arsenic exposure in random urine specimens

**Interpretation:** Normally, humans consume 5 to 25 mcg of arsenic each day as part of their normal diet; therefore, normal urine arsenic output is less than 35 mcg arsenic per gram creatinine (<35 mcg/g). When exposed to inorganic arsenic, the urine output may be above 1,000 mcg/g and remain elevated for weeks. After a seafood meal (seafood contains a nontoxic, organic form of arsenic), on the other hand, the urine output of arsenic may be above 200 mcg/g, after which it will decline to under 35 mcg/g over a period of 1 to 2 days. Exposure to inorganic arsenic, the toxic form of arsenic, causes prolonged excretion of arsenic in the urine for many days. Urine excretion rates above 1,000 mcg/g indicates significant exposure. The highest value observed at Mayo Clinic was 450,000 mcg/L in a patient with severe symptoms of gastrointestinal distress, shallow breathing with classic "garlic breath," intermittent seizure activity, cardiac arrhythmias, and later onset of peripheral neuropathy.

**Reference Values:**
Only orderable as part of profile. See ARSCR / Arsenic/Creatinine Ratio, with Reflex, Random, Urine or HMCRU / Heavy Metal/Creatinine Ratio, with Reflex, Urine.

**Clinical References:**

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**Arsenic/Creatinine, with Reflex, Random, Urine**

**Clinical Information:** Arsenic is perhaps the best known of the metal toxins, having gained notoriety from its extensive use by Renaissance nobility as an antisyphilitic agent and, paradoxically, as an antidote against acute arsenic poisoning. Even today, arsenic is still 1 of the more common toxicants found in insecticides, and leaching from bedrock to contaminate groundwater. The toxicity of arsenic is due to 3 different mechanisms, 2 of them related to energy transfer. Arsenic covalently and avidly binds to dihydrolipoic acid, a necessary cofactor for pyruvate dehydrogenase. Absence of the cofactor inhibits the conversion of pyruvate to acetyl coenzyme A, the first step in gluconeogenesis. This results in loss of energy supply to anaerobic cells, the predominant mechanism of action of arsenic on neural cells that rely on anaerobic respiration for energy. Neuron cell death is due to an inability to make ATP, the predominant mechanism of action of arsenic on neural cells that rely on anaerobic respiration for energy. Neuron cell death occurs after long-term energy loss results in bilateral peripheral neuropathy. Arsenic also competes with phosphate for binding to adenosine triphosphate during its synthesis by mitochondria via oxidative phosphorylation, causing formation of the lower energy adenosine diphosphate monoarsine. This results in loss of energy supply to aerobic cells. Cardiac cells are particularly sensitive to this form of energy loss; fatigue due to poor cardiac output is a common symptom of arsenic exposure. Arsenic furthermore binds avidly with any hydrated sulfhydryl group on protein, distorting the 3-dimensional configuration of that protein, causing it to lose activity. Interaction of arsenic with epithelial cell protein at the sites of highest physiologic concentration, the small intestine and proximal tubule of the kidney, results in cellular degeneration. Epithelial cell erosion in the gastrointestinal tract and proximal tubule are characteristic of arsenic toxicity. Arsenic is also a known carcinogen, but the mechanism of this effect is not definitively known. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status.
Changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can occur. Arsenic exists in a number of different forms; organic forms are nontoxic, inorganic forms are toxic. See ASFRU / Arsenic Fractionation, Random, Urine for details about arsenic forms. Because arsenic is excreted predominantly by glomerular filtration, analysis for arsenic in urine is the best screening test to detect arsenic exposure.

**Useful For:** Preferred screening test for detection of arsenic exposure in random urine specimens

**Interpretation:** Normally, humans consume 5 to 25 mcg of arsenic each day as part of their normal diet; therefore, normal urine arsenic output is less than 35 mcg arsenic per gram creatinine (<35 mcg/g). When exposed to inorganic arsenic, the urine output may be above 1,000 mcg/g and remain elevated for weeks. After a seafood meal (seafood contains a nontoxic, organic form of arsenic), on the other hand, the urine output of arsenic may be above 200 mcg/g, after which it will decline to under 35 mcg/g over a period of 1 to 2 days. Exposure to inorganic arsenic, the toxic form of arsenic, causes prolonged excretion of arsenic in the urine for many days. Urine excretion rates above 1,000 mcg/g indicates significant exposure. The highest value observed at Mayo Clinic was 450,000 mcg/L in a patient with severe symptoms of gastrointestinal distress, shallow breathing with classic “garlic breath,” intermittent seizure activity, cardiac arrhythmias, and later onset of peripheral neuropathy.

**Reference Values:**

- 0-17 years: not established
- > or =18 years: <24 mcg/g creatinine


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**Artichoke (Cynara scolymus) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35

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**Arylsulfatase A, 24 Hour, Urine**

**Clinical Information:** Metachromatic leukodystrophy (MLD) is a lysosomal storage disorder caused by a deficiency of the arylsulfatase A (ARSA) enzyme, which leads to the accumulation of galactosyl sulfatide (cerebroside sulfate) in the white matter of the central nervous system and in the peripheral nervous system. Galactosyl sulfatide and, to a smaller extent, lactosyl sulfatide, also accumulate within the kidney, gallbladder, and other visceral organs and are excreted in excessive amounts in the urine. The 3 clinical forms of MLD are late-infantile, juvenile, and adult, depending on age of onset. All result in progressive neurologic changes and leukodystrophy demonstrated on magnetic resonance imaging. Late-infantile MLD is the most common (50%-60% of cases) and usually presents between age 1 to 2 years with hypotonia, clumsiness, diminished reflexes, and slurred speech. Progressive neurodegeneration occurs and most patients die within 5 years of the diagnosis. Juvenile MLD (20%-30% of cases) is characterized by onset between 4 to 14 years. Presenting features are behavior problems, declining school performance, clumsiness, and slurred speech. Progressive neurodegeneration occurs at a somewhat slower and more variable rate than the late-infantile form. Adult MLD (15%-20% of cases) has an onset after puberty and can be as late as the fourth or fifth decade. Presenting features are often behavior and personality changes, including psychiatric symptoms. Clumsiness, neurologic symptoms, and seizures are also common. The
disease course has variable progression and may occur over 2 to 3 decades. The disease prevalence is estimated to be approximately 1 in 100,000. MLD is an autosomal recessive disorder and is caused by mutations in the ARSA gene coding for the ARSA enzyme. This disorder is distinct from conditions caused by deficiencies of arylsulfatase B (Maroteaux-Lamy disease) and arylsulfatase C (steroid sulfatase deficiency). Saposin B deficiency is a rare autosomal recessive disorder with symptoms that mimic MLD; however ARSA enzyme level is normal. Like MLD, patients with saposin B deficiency can also excrete excessive amounts of sulfatides in their urine. Individuals with multiple sulfatase deficiency, which is clinically distinct from MLD, will also have deficiency of arylsulfatase A. Extremely low ARSA levels have been found in some clinically normal parents and other relatives of MLD patients. These individuals do not have metachromatic deposits in peripheral nerve tissues, and their urine content of sulfatide is normal. Individuals with this "pseudodeficiency" have been recognized with increasing frequency among patients with other apparently unrelated neurologic conditions as well as among the general population. This has been associated with a fairly common polymorphism in the ARSA gene which leads to low expression of the enzyme (5%-20% of normal). These patients can be difficult to differentiate from actual MLD patients. Additional studies, such as molecular genetic testing of ARSA (ARSAZ / ARSA Gene, Full Gene Analysis), urinary excretion of sulfatides (CTSA / Ceramide Trihexosides and Sulfatides, Urine), and/or histological analysis for metachromatic lipid deposits in nervous system tissue are recommended to confirm a diagnosis. Current treatment options for MLD are focused on managing disease manifestations such as seizures. Bone marrow transplantation remains controversial, and the effectiveness of enzyme replacement therapy may be limited due to difficulties crossing the blood-brain barrier. Other treatments under ongoing investigation include hematopoietic stem cell transplantation and fetal umbilical cord blood transplantation.

Useful For: Detection of metachromatic leukodystrophy in urine specimens

Interpretation: Greatly reduced levels of arylsulfatase A in urine (< or =15 nmol/h/mL), as well as in serum and various tissues, is seen in patients with metachromatic leukodystrophy. Individuals with pseudoarylsulfatase A deficiency can have results in the affected range, but are otherwise unaffected with metachromatic leukodystrophy. Abnormal results should be confirmed using CTSA / Ceramide Trihexosides and Sulfatides, Urine. If molecular confirmation is desired, consider molecular genetic testing ARSAZ / ARSA Gene, Full Gene Analysis.

Reference Values:
> or =19 nmol/h/mL

Note: Results from this assay may not reflect carrier status because of individual variation of arylsulfatase A enzyme levels.

Clinical References:
resonance imaging. Late-infantile MLD is the most common (50%-60% of cases) and usually presents between 6 months to 2 years of age with hypotonia, clumsiness, diminished reflexes, and slurred speech. Progressive neurodegeneration occurs with most patients dying within 5 years of the diagnosis. Juvenile MLD (20%-30% of cases) is characterized by onset between 4 to 14 years. Presenting features are behavior problems, declining school performance, clumsiness, and slurred speech. Neurodegeneration occurs at a somewhat slower and more variable rate than the late-infantile form. Adult MLD (15%-20% of cases) has an onset after puberty and can be as late as the fourth or fifth decade. Presenting features are often behavior and personality changes, including psychiatric symptoms. Clumsiness, neurologic symptoms, and seizures are also common. The disease course has variable progression and may occur over 2 to 3 decades. The disease prevalence is estimated to be approximately 1 in 100,000. MLD is an autosomal recessive disorder and is caused by mutations in the ARSA gene coding for the ARSA enzyme. This disorder is distinct from conditions caused by deficiencies of arylsulfatase B (Maroteaux-Lamy disease) and arylsulfatase C (steroid sulfatase deficiency). Saposin B deficiency is a rare autosomal recessive disorder with symptoms that mimic MLD; however, ARSA enzyme level is normal. Like MLD, patients with saposin B deficiency can also excrete excessive amounts of sulfatides in their urine. Individuals with multiple sulfatase deficiency, which is clinically distinct from MLD, will also have deficiency of arylsulfatase A. Extremely low ARSA levels have been found in some clinically normal parents and other relatives of MLD patients. These individuals do not have metachromatic deposits in peripheral nerve tissues, and their urine content of sulfatide is normal. Individuals with this "pseudodeficiency" have been recognized with increasing frequency among patients with other apparently unrelated neurologic conditions as well as among the general population. This has been associated with fairly common polymorphisms in the ARSA gene, which leads to low expression of the enzyme (5%-20% of normal). These patients can be difficult to differentiate from actual MLD patients. Additional studies, such as molecular genetic testing of ARSA (ARSAZ / ARSA Gene, Full Gene Analysis), urinary excretion of sulfatides (CTSA / Ceramide Trihexosides and Sulfatides, Urine), and histological analysis for metachromatic lipid deposits in nervous system tissue are recommended to confirm a diagnosis. Current treatment options for MLD are focused on managing disease manifestations such as seizures. Bone marrow transplantation remains controversial, and the effectiveness of enzyme replacement therapy may be limited due to difficulties crossing the blood-brain barrier. Other treatments under ongoing investigation include hematopoietic stem cell transplantation and fetal umbilical cord blood transplantation.

Useful For: Preferred test for detection of metachromatic leukodystrophy

Interpretation: Decreased enzyme levels indicate an individual is affected with metachromatic leukodystrophy (MLD). Note that individuals with pseudodeficiency of arylsulfatase A can have results in this range, but are otherwise unaffected with MLD. Abnormal results should be confirmed using CTSA / Ceramide Trihexosides and Sulfatides, Urine. If molecular confirmation is desired, consider molecular genetic testing ARSAZ / ARSA Gene, Full Gene Analysis.

Reference Values:
> or =62 nmol/h/mg

Note: Results from this assay may not reflect carrier status because of individual variation of arylsulfatase A enzyme levels. Low normal values may be due to the presence of pseudodeficiency gene or carrier gene. Patients with these depressed levels may be phenotypically normal.

Arylsulfatase B, Fibroblasts

Clinical Information: Mucopolysaccharidosis VI (MPS VI; Maroteaux-Lamy syndrome) is an autosomal recessive lysosomal storage disorder caused by the deficiency of N-acetylgalactosamine 4-sulfatase, also known as arylsulfatase B (ARSB). The mucopolysaccharidoses are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of complex macromolecules called glycosaminoglycans (GAGs) including dermatan sulfate, heparan sulfate, keratan sulfate, and chondroitin sulfate. Accumulation of GAGs (also called mucopolysaccharides) in lysosomes interferes with normal functioning of cells, tissues, and organs. Clinical features and severity of symptoms are widely variable, but typically include short stature, dysostosis multiplex, facial dysmorphism, stiff joints, hepatosplenomegaly, corneal clouding, and cardiac disease. Intelligence is usually normal. Rapidly progressing forms have an early onset of symptoms, significantly elevated GAGs, and can lead to death before the second or third decades. A more slowly progressing form has a later onset, milder skeletal manifestations, smaller elevations of GAGs, and typically a longer lifespan. Estimates of the incidence of MPS VI range from 1 in 250,000 to 1 in 300,000. Treatment options include hematopoietic stem cell transplantation and/or enzyme replacement therapy. A diagnostic workup in an individual with MPS VI typically demonstrates elevated levels of urinary GAGs and increased dermatan sulfate detected on thin-layer chromatography. Reduced or absent activity of ARSB in leukocytes and/or fibroblasts is suggestive of a diagnosis of MPS VI. Sequencing of the ARSB gene allows for detection of disease-causing mutations in affected patients and identification of familial mutations allows for testing of at-risk family members (MPS6Z / Mucopolysaccharidosis VI, Full Gene Analysis). Currently, no clear genotype-phenotype correlations have been established. ARSB activity is also reduced in 2 other rare autosomal recessive disorders, multiple sulfatase deficiency (MSD) and mucolipidosis II (I-cell disease). Both of these conditions present with developmental delays that make them clinically different from MPS VI. The symptoms of MSD mimic metachromatic leukodystrophy (MLD) as well as the mucopolysaccharidoses and can include developmental delay, neurologic regression, dysmorphic facies, dysostosis multiplex, organomegaly, ichthyosis, and chondroplasia punctata. If MSD is suspected, testing of an additional sulfatase enzyme, such as arylsulfatase A in MLD, can help determine if multiple sulfatases are deficient. I-cell disease is characterized by congenital or early infantile manifestations including coarse facial features, short stature, skeletal anomalies, cardio- and hepatomegaly, and developmental delays. This is a progressive disorder and death typically occurs in the first decade of life. Additional testing including hydrolase enzymes in serum, such as hexosaminidase A in Tay-Sach disease, is recommended if a diagnosis of I-cell is suspected.

Useful For: Diagnosis of mucopolysaccharidosis VI (Maroteaux-Lamy syndrome)

Interpretation: Arylsulfatase B is deficient in mucopolysaccharidosis VI, multiple sulfatase deficiency, and mucolipidosis II.

Reference Values: > or =6.08 nmol/min/mg protein


Ascaris, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from...
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class I or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**VITC 42362**

**Ascorbic Acid (Vitamin C), Plasma**

**Clinical Information:** Vitamin C, also known as L-ascorbic acid or simply ascorbic acid, is a water-soluble vitamin that is naturally present in some foods, added to others, and available as a dietary supplement. Humans, unlike most animals, are unable to synthesize vitamin C endogenously, so it is an essential dietary component. Vitamin C is required for the enzymatic amidation of neuropeptides, production of adrenal cortical steroid hormones, promotion of the conversion of tropocollagen to collagen, and metabolism of tyrosine and folate. It also plays a role in lipid and vitamin metabolism and is a powerful reducing agent or antioxidant. Specific actions include: activation of detoxifying enzymes in the liver, antioxidation, interception and destruction of free radicals, preservation and restoration of the antioxidant potential of vitamin E, and blockage of the formation of carcinogenic nitrosamines. In addition, vitamin C appears to function in a variety of other metabolic processes in which its role has not been well characterized. Prolonged deficiency of vitamin C leads to the development of scurvy, a disease characterized by an inability to form adequate intercellular substance in connective tissues. This results in the formation of swollen, ulcerative lesions in the gums, mouth, and other tissues that are structurally weakened. Early symptoms may include weakness, easy fatigue and listlessness, as well as shortness of breath, and aching joints, bones, and muscles. The need for vitamin C can be increased by the use of
aspirin, oral contraceptives, tetracycline, and a variety of other medications. Psychological stress and advancing age also tend to increase the need for vitamin C. Among the elderly, lack of fresh fruit and vegetables often adds vitamin C depletion to the inherently increased need, with development of near-scurvy status.

**Useful For:** Diagnosing vitamin C deficiency As an aid to deter excessive intake

**Interpretation:** Values below 0.2 mg/dL indicate significant deficiency. Values greater than or equal to 0.2 mg/dL and less than 0.4 mg/dL are consistent with a moderate risk of deficiency due to inadequate tissue stores. Values of 0.4 to 2.0 mg/dL indicate adequate supply. The actual level at which vitamin C is excessive has not been defined. Values above 3.0 mg/dL are suggestive of excess intake. Whether vitamin C in excess is indeed toxic continues to be uncertain. However, limited observations suggest that this condition may induce uricosuria and, in individuals with glucose-6-phosphate dehydrogenase deficiency, may induce increased red blood cell fragility.

**Reference Values:**
0.4-2.0 mg/dL

**Clinical References:**

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**Ashkenazi Jewish Mutation Analysis Panel Without Cystic Fibrosis (CF)**

**Clinical Information:** Certain genetic diseases are more common in individuals of Ashkenazi Jewish heritage (Jewish individuals of Eastern European ancestry) compared to the non-Jewish population. The majority of these conditions are inherited in an autosomal recessive manner. This group of diseases includes Gaucher, Tay-Sachs, familial dysautonomia, Canavan, mucolipidosis IV, Niemann-Pick Type A and B, FANCC-related Fanconi anemia, and Bloom syndrome. While these conditions are observed outside of the Ashkenazi Jewish population, they occur at a lower frequency. It is estimated that an individual of Ashkenazi Jewish ancestry has a 20% to 25% chance of being a carrier of 1 of these diseases. Gaucher Disease: Gaucher disease is a relatively rare lysosomal storage disorder resulting from a deficiency of acid beta-glucocerebrosidase. Mutations in the beta-glucocerebrosidase gene, GBA, cause the clinical manifestations of Gaucher disease. There are 3 major types of Gaucher disease: nonneuropathic (type 1), acute neuropathic (type 2), and subacute neuropathic (type 3). Type 1 accounts for over 95% of all cases of Gaucher disease and is the presentation commonly found among Ashkenazi Jewish patients. Type 1 disease does not involve nervous system dysfunction; patients display anemia, low blood platelet levels, massively enlarged livers and spleens, lung infiltration, and extensive skeletal disease. There is a broad spectrum of disease in type 1, with some patients exhibiting severe symptoms and others very mild disease. Types 2 and 3 are associated with neurological disease of variable onset and progression, though type 2 tends to be more severe. Eight common GBA mutations, including the N370S mutation most commonly found in the Ashkenazi Jewish population, are included in this test: delta55bp, V394L, N370S, IVS2+1G->A, 84G->GG, R496H, L444P, and D409H. Tay-Sachs: Tay-Sachs disease is caused by an absence of hexosaminidase (HexA) enzyme activity, which results in the accumulation of the sphingolipid GM2 ganglioside. Mutations in the HEXA gene cause the clinical manifestations of Tay-Sachs disease (TSD). The most common form of TSD becomes apparent in infancy when mild motor weakness is noted along with impaired visual acuity and the presence of a "startle response." Other manifestations of this condition include progressive neurodegeneration, seizures, and blindness, leading to total incapacitation and death. This panel tests for the 3 common mutations in the Ashkenazi Jewish population: 1278insTATC, G269S, and IVS12+1G->C. Also included in this assay are the mutations IVS9+1G->A and delta7,6kb mutations along with the R247W and R249W polymorphisms associated with pseudodeficiency. Familial Dysautonomia: Familial dysautonomia affects sensory, parasympathetic, and sympathetic neurons.
Patients experience gastrointestinal dysfunction, pneumonia, vomiting episodes, altered sensitivity to pain and temperature, and cardiovascular problems. Progressive neuronal degeneration continues throughout the lifespan. Mutations in the IKBKAP gene cause the clinical manifestations of familial dysautonomia. Two mutations in the IKBKAP gene are common in the Ashkenazi Jewish population: IVS20(+6)T>C and R696P. Canavan Disease: Canavan disease is a severe leukodystrophy resulting from a deficiency of the enzyme aspartoacylase. Mutations in the ASPA gene cause the clinical manifestations of Canavan disease. The deficiency of aspartoacylase leads to spongy degeneration of the brain, and the disease is characterized by delayed development beginning at age 3 to 6 months, head lag, macrocephaly, and hypotonia. Death usually occurs in the first decade of life. Four ASPA mutations are included in this test: 433(-2)A>G, A305E, E285A, and Y231X. Mucolipidosis IV: Mucolipidosis IV is a lysosomal storage disease characterized by mental retardation, hypotonia, corneal clouding, and retinal degeneration. Mutations in the MCOLN1 gene are responsible for the clinical manifestations of mucolipidosis IV. Two mutations in the MCOLN1 gene account for the majority of mutations in the Ashkenazi Jewish population: IVS3(-2)A>G and delta6.4kb. Niemann-Pick Disease Types A and B: Niemann-Pick disease (types A and B) is a lysosomal storage disease caused by a deficiency of the enzyme acid sphingomyelinase. The clinical presentation of type A disease is characterized by jaundice, progressive loss of motor skills, feeding difficulties, learning disabilities, and hepatosplenomegaly. Death usually occurs by age 3. Type B disease is milder, though variable in its clinical presentation. Most individuals with type B do not have neurologic involvement and survive to adulthood. Mutations in the SMPD1 gene are known to cause Niemann-Pick disease types A and B. There are 3 common mutations causing Niemann-Pick type A in the Ashkenazi Jewish population: L302P, R496L, and fsP330. The deltaR608 mutation accounts for approximately 90% of the type B mutant alleles in individuals from the Maghreb region of North Africa and 100% of the mutation alleles in Gran Canaria Island. Fanconi Anemia: Fanconi anemia is an aplastic anemia that leads to bone marrow failure and myelodysplasia or acute myelogenous leukemia. Physical findings include short stature; upper limb, lower limb, and skeletal malformations; and abnormalities of the eyes and genitourinary tract. Mutations in several genes have been associated with Fanconi anemia, although 1 mutation, IVS4(+4)A>T, in the FANCC gene is common in the Ashkenazi Jewish population. A second mutation, 322delG, is over represented in FANCC patients of Northern European ancestry. Bloom Syndrome: Bloom syndrome is characterized by short stature, sun sensitivity, susceptibility to infections, and a predisposition to cancer. Mutations in the BLM gene lead to genetic instability (increased chromosomal breakage and sister chromatid exchange) and cause the clinical manifestations of Bloom syndrome. The protein encoded by the BLM gene is a helicase involved in maintaining DNA integrity. There is a common mutation in the Ashkenazi Jewish population: 2281delATCTGAlnsTAGATTCA (2281del16ins7). Because of the high sensitivity of carrier testing in the Ashkenazi Jewish population, the American College of Medical Genetics and Genomics (ACMG) recommends that carrier screening for cystic fibrosis (CF), Canavan, Tay-Sachs, familial dysautonomia, Niemann-Pick type A, Fanconi anemia (FANCC), Bloom syndrome, mucolipidosis IV, and Gaucher disease be offered to individuals of Ashkenazi Jewish ancestry. The mutation detection rates and carrier frequencies for the diseases included in this panel are listed below. Of note, testing for CF is not included in this panel. If testing for this disorder is desired, please see details and ordering information under CFP / Cystic Fibrosis Mutation Analysis, 106-Mutation Panel. Disease Carrier Rate in the AJ Population Mutation Detection Rate Gaucher 1/18 95% Tay-Sachs 1/31 *99% Familial dysautonomia 1/31 99% Canavan 1/41 98% Mucolipidosis IV 1/127 95% Niemann-Pick type A/B 1/90 97% FANCC-related Fanconi anemia 1/89 >99% Bloom syndrome 1/107 >99% *with biochemical testing The Ashkenazi Jewish panel is useful for identifying carriers of these 8 conditions in an at-risk population. Because the diseases included in the panel are inherited in an autosomal recessive manner, the presence of a family history is not a prerequisite for testing consideration. The identification of disease-causing mutations allows for carrier testing of at-risk family members and prenatal diagnosis for pregnancies in which both parents are known carriers. Refer to Carrier Testing for Tay-Sachs Disease and Other GM2 Gangliosidosis Variants: Supplementing Traditional Biochemical Testing with Molecular Methods, Mayo Medical Laboratories Communique 2004 Jul;29(7) for more information regarding diagnostic strategy. Of note, approximately 1 in 25 individuals of Ashkenazi Jewish ancestry are also carriers of cystic fibrosis (CF). Therefore, the American College of Medical Genetics also recommends that carrier screening for CF be offered to individuals of Ashkenazi Jewish ancestry who are pregnant or considering pregnancy. Carrier screening for CF is available by ordering CFP / Cystic Fibrosis Mutation Analysis, 106-Mutation Panel.
Useful For: Carrier screening in individuals of Ashkenazi Jewish ancestry for Bloom syndrome, Canavan disease, FANCC-related Fanconi anemia, familial dysautonomia, Gaucher disease, mucolipidosis IV, Niemann-Pick disease types A and B, and Tay-Sachs disease

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.


ASPAR 82478

Asparagus, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.

Aspartate Aminotransferase (AST) (GOT), Serum

**Clinical Information:** Aspartate aminotransferase (AST) is found in high concentrations in liver, heart, skeletal muscle, and kidney. AST is present in both cytoplasm and mitochondria of cells. In cases involving mild tissue injury, the predominant form of AST is that from the cytoplasm. Severe tissue damage results in more of the mitochondrial enzyme being released. High levels of AST can be found in cases such as myocardial infarction, acute liver cell damage, viral hepatitis, and carbon tetrachloride poisoning. Slight to moderate elevation of AST is seen in muscular dystrophy, dermatomyositis, acute pancreatitis, and crushed muscle injuries.

**Useful For:** Diagnosing and monitoring liver disease, particularly diseases resulting in a destruction of hepatocytes

**Interpretation:** Elevated aspartate aminotransferase (AST) values are seen in parenchymal liver diseases characterized by a destruction of hepatocytes. Values are typically at least 10 times above the normal range. Levels may reach values as high as 100 times the upper reference limit, although 20- to 50-fold elevations are most frequently encountered. In infectious hepatitis and other inflammatory conditions affecting the liver, alanine aminotransferase (ALT) is characteristically as high as or higher than AST, and the ALT:AST ratio, which normally and in other condition is less than 1, becomes greater than unity. AST levels are usually elevated before clinical signs and symptoms of disease appear. Five- to 10-fold elevations of both AST and ALT occur in patients with primary or metastatic carcinoma of the liver, with AST usually being higher than ALT, but levels are often normal in the early stages of malignant infiltration of the liver. Elevations of ALT activity persist longer than do those of AST activity. Elevated AST values may also be seen in disorders affecting the heart, skeletal muscle, and kidney.

**Reference Values:**
Males
- 0-11 months: not established
- 1-13 years: 8-60 U/L
- > or =14 years: 8-48 U/L
Females
- 0-11 months: not established
- 1-13 years: 8-50 U/L
- > or =14 years: 8-43 U/L


Aspen (Populus tremuloides) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:** <0.35 kU/L

Aspergillus (Galactomannan) Antigen, Serum

**Clinical Information:** Invasive aspergillosis (IA) is a severe infection that occurs in patients with prolonged neutropenia, following transplantation or in conjunction with aggressive immunosuppressive regimens (eg, prolonged corticosteroid usage, chemotherapy). The incidence of IA is reported to vary from 5% to 20% depending on the patient population. IA has an extremely high mortality rate of 50% to 80% due in part to the rapid progression of the infection (ie, 1-2 weeks from onset to death). Approximately 30% of cases remain undiagnosed and untreated at death. Definitive diagnosis of IA requires histopathological evidence of deep-tissue invasion or a positive culture. However, this evidence is often difficult to obtain due to the critically ill nature of the patient and the fact that severe
thrombocytopenia often precludes the use of invasive procedures to obtain a quality specimen. The sensitivity of culture in this setting also is low, reportedly ranging from 30% to 60% for bronchoalveolar lavage fluid. Accordingly, the diagnosis is often based on nonspecific clinical symptoms (unexplained fever, cough, chest pain, dyspnea) in conjunction with radiologic evidence (computed tomography: CT scan); and definitive diagnosis is often not established before fungal proliferation becomes overwhelming and refractory to therapy. Recently, a serologic assay was approved by the FDA for the detection of galactomannan, a molecule found in the cell wall of Aspergillus species. Serum galactomannan can often be detected a mean of 7 to 14 days before other diagnostic clues become apparent, and monitoring of galactomannan can potentially allow initiation of preemptive antifungal therapy before life-threatening infection occurs.

**Useful For:** Aiding in the diagnosis of invasive aspergillosis Assessing response to therapy

**Interpretation:** A positive result supports a diagnosis of invasive aspergillosis (IA). Positive results should be considered in conjunction with other diagnostic procedures, such as microbiologic culture, histological examination of biopsy specimens, and radiographic evidence. See Cautions. A negative result does not rule out the diagnosis of IA. Repeat testing is recommended if the result is negative but IA is suspected. Patients at risk of IA should have a baseline serum tested and should be monitored twice a week for increasing galactomannan antigen levels. Galactomannan antigen levels may be useful in the assessment of therapeutic response. Antigen levels decline in response to antimicrobial therapy.

**Reference Values:**

<0.5 index
Reference values apply to all ages.


**FASP**

**Aspergillus Antibodies, Immunodiffusion, Serum**

**Reference Values:**

Aspergillus flavus Ab
Aspergillus niger Ab
Aspergillus fumigatus Ab

Reference Range: Negative

**Interpretive Criteria:**

- Negative: Antibody not detected
- Positive: Antibody detected

A positive result is represented by 1 or more precipitin bands, and may indicate fungus ball, allergic bronchopulmonary aspergillosis (ABA) or invasive aspergillosis. Generally, the appearance of 3 â€“ 4 bands indicates either fungus ball or ABA.

**ASPBA**

**Aspergillus Antigen, Bronchoalveolar Lavage**

**Clinical Information:** Invasive aspergillosis (IA) is a severe infection that occurs in patients with...
prolonged neutropenia following transplantation or in conjunction with aggressive immunosuppressive regimens (eg, prolonged corticosteroid use, chemotherapy). The incidence of IA is reported to vary from 5% to 20% depending on the patient population. IA has an extremely high mortality rate of 50% to 80%, due in part to the rapid progression of the infection (ie, 1-2 weeks from onset to death). Approximately 30% of cases remain undiagnosed and untreated at death. Definitive diagnosis of IA requires histopathological evidence of deep-tissue invasion or a positive culture. However, this evidence is often difficult to obtain due to the critically ill nature of the patient and the fact that severe thrombocytopenia often precludes the use of invasive procedures to obtain a quality specimen. The sensitivity of culture in this setting also is low, reportedly ranging from 30% to 60% for bronchoalveolar lavage (BAL) fluid. Accordingly, the diagnosis is often based on nonspecific clinical symptoms (unexplained fever, cough, chest pain, dyspnea) in conjunction with radiologic evidence (computed tomography scan), and a definitive diagnosis is often not established before fungal proliferation becomes overwhelming and refractory to therapy. Recently, a serologic assay was approved by the FDA for the detection of galactomannan, a molecule found in the cell wall of Aspergillus species. Serum galactomannan (Aspergillus antigen) can often be detected a mean of 7 to 14 days before other diagnostic clues become apparent, and monitoring of Aspergillus antigen can potentially allow initiation of preemptive antifungal therapy before life-threatening infection occurs. The clinical utility of Aspergillus antigen testing in BAL specimens as an early prognostic indicator of IA has recently been assessed. These studies demonstrated equivalent or higher sensitivity compared to detection of Aspergillus antigen in serum. This assay may be useful in the assessment of therapeutic response as antigen levels typically decline in response to effective antimicrobial therapy.

**Useful For:** Aids in the diagnosis of invasive aspergillosis and assessing response to therapy

**Interpretation:** A positive result in bronchoalveolar lavage (BAL) fluid supports a diagnosis of invasive, pulmonary aspergillosis. Positive results should be considered in conjunction with other diagnostic procedures, such as microbiologic culture, histological examination of biopsy specimens, and radiographic evidence (see Cautions). A negative result in BAL fluid does not rule out the diagnosis of invasive aspergillosis (IA). Patients at risk of IA should be monitored twice a week for Aspergillus antigen levels in serum until determined to be clinically unnecessary. Aspergillus antigen levels typically decline in response to effective antimicrobial therapy.

**Reference Values:**

<0.5 Index

**Clinical References:**


**Aspergillus flavus IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35–0.69 Low Positive 2 0.70–3.49 Moderate Positive 3 3.50–17.50 Positive 4 17.50–49.99 Strong Positive 5 50.00–99.99 Very Strong Positive 6 >99.99 Very Very Strong Positive

**Reference Values:**

<0.35 kU/L
Aspergillus fumigatus, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


Aspergillus fumigatus, IgG Antibodies, Serum

Clinical Information: Aspergillus fumigatus is one of the causative agents of hypersensitivity pneumonitis (HP), as well as invasive lung disease with cavitation or pneumonitis and allergic bronchopulmonary disease.(1) Other causative microorganisms of HP include Micropolyspora faeni and Thermoactinomyces vulgaris. The development of HP and allergic bronchopulmonary disease caused by Aspergillus fumigatus is accompanied by an immune response to Aspergillus fumigatus antigens with production of IgG or IgE antibodies, respectively. While the immunopathogenesis of HP and allergic bronchopulmonary disease is not known, several immune mechanisms are postulated to play a role, including both cellular and humoral mechanisms.

Useful For: Evaluation of patients suspected of having lung disease caused by Aspergillus fumigatus

Interpretation: Elevated concentrations of IgG antibodies to Aspergillus fumigatus,
Thermoactinomyces vulgaris, or Micropolyspora faeni in patients with signs and symptoms of hypersensitivity pneumonitis may be consistent with disease caused by exposure to 1 or more of these organic antigens.

**Reference Values:**
- <4 years: not established
- > or =4 years: < or =102 mg/L

**Clinical References:**

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**FAGPP 57903**

**Aspergillus IgG Precipitins Panel**

**Interpretation:** The gel diffusion method was used to test this patients serum for the presence of precipitating antibodies (IgG) to the antigens indicated. These antibodies are serological markers for exposure and immunological sensitization. The clinical significance varies, depending on the history and symptoms.

**Reference Values:**
- Negative

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**ASPG 86324**

**Aspergillus niger, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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ADMA
Asymmetric Dimethylarginine, Plasma

Clinical Information: Asymmetric dimethylarginine (ADMA) is an independent risk factor for coronary heart disease. ADMA inhibits nitric oxide (NO) synthesis and is elevated in diseases related to endothelial dysfunction including hypertension, hyperlipidemia, and type-II diabetes mellitus. Elevation in ADMA and subsequent NO synthesis inhibition leads to vasoconstriction, reduced peripheral blood flow, and reduced cardiac output. Elevated plasma ADMA confers a 4- to 6-fold increased risk of subsequent cardiovascular events or mortality among patients with acute coronary syndrome, unstable angina, type-II diabetes mellitus, end-stage renal disease, and coronary heart disease. Among patients with coronary heart disease, baseline ADMA remained a significant risk factor of adverse events even after adjusting for LDL-C, HDL-C, triglycerides, creatinine and high sensitivity C-reactive protein. Plasma ADMA concentrations are lowered by rosuvastatin and atorvastatin, but not simvastatin in patients with hypercholesterolemia. Addition of vildagliptin (Galvus) to metformin significantly reduced ADMA concentrations among patients with type-II diabetes mellitus.

Useful For: An adjunct to other risk markers for assessing an individual's likelihood of future coronary events, in patients with coronary heart disease, type-II diabetes mellitus, or kidney disease

Interpretation: In patients with pre-existing coronary conditions or at high risk for coronary events (diabetes, renal insufficiency), asymmetric dimethylarginine (ADMA) levels in the upper tertile, >112 ng/mL, confer an increased risk for future coronary events. Reductions in ADMA are not known to be predictive of decreased risk of future coronary effects.

Reference Values:
<18 years: not established
> or =18 years: 63-137 ng/mL

**ATRX Immunostain, Technical Component Only**

**Clinical Information:** This test is intended to identify the presence of ATP-dependent helicase ATRX, X-linked helicase II (ATRX) protein. ATRX is produced by most mitotically active normal cells and can be useful in the distinction of differentiated from undifferentiated neoplasms.

**Useful For:** Distinguishing differentiated from undifferentiated neoplasms

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Atypical Hemolytic Uremic Syndrome (aHUS) Complement Panel, Serum and Plasma**

**Clinical Information:** Individuals presenting with thrombotic microangiopathies (TMAs) require clinical testing to identify the underlying cause. Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are both acute syndromes with many overlapping clinical features. Reduced levels of ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motives) activity is associated with TTP and is one laboratory feature that distinguishes TTP from HUS. HUS can also have a number of causes; one of the rarer forms of disease is caused by defects in the alternative pathway of the complement system, so called atypical-HUS (aHUS). Patients with defective alternative pathway regulation can benefit from biologics that suppress the complement system. The purpose of this panel is to aid in the differential diagnosis of TMAs. The suggested approach is to rule-out other causes of TMAs first, since aHUS is one of the rarer causes of TMAs. Additionally, the assays can be used in the setting of membranoproliferative glomerulonephritis (MPGN), and help distinguish between immune-complex mediated or complement-mediated kidney disease. MPGN mediated by immune-complexes are the ones resulting from infectious processes, autoimmune diseases, or monoclonal gammopathies, whereas complement-mediated MPGN can then be subdivided in C3 glomerulonephritis (C3GN) and dense deposit disease (DDD), based on electron microscopy of the kidney biopsy histological findings. Despite phenotypic differences, these glomerular diseases share dysfunction of the alternative pathway as the defining pathophysiology.

**Useful For:** Detecting deficiencies in the alternative pathway that can cause atypical-hemolytic uremic syndrome, dense deposit disease, and C3 glomerulonephritis A second-order test that aids in the differential diagnosis of thrombotic microangiopathies

**Interpretation:** An interpretive report will be included.

**Reference Values:**
FACTOR B COMPLEMENT ANTIGEN
15.2-42.3 mg/dL

SC5b-9 COMPLEMENT
< or =250 ng/mL

FACTOR H COMPLEMENT ANTIGEN
23.6-43.1 mg/dL

C4d COMPLEMENT ACTIVATION FRAGMENT
< or =9.8 mcg/mL

CBb COMPLEMENT ACTIVATION FRAGMENT
< or =1.6 mcg/mL

COMPLEMENT C4
14-40 mg/dL

COMPLEMENT C3
75-175 mg/dL

COMPLEMENT, ALTERNATE PATHWAY (AH50), FUNCTIONAL
> or =46% normal

COMPLEMENT, TOTAL
> or =16 years: 30-75 U/mL

Reference values have not been established for patients who are <16 years of age.

Clinical References:

FAPPN
57142

Atypical Pneumonia DNA Panel Qual
Reference Values:
Reference Range: Not detected

AUPU
82855

Aureobasidium pullulans, IgE

Clinical Information:
Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For:
Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm
sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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Reference values apply to all ages.


**Australian Pine, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>Class</th>
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**Reference values apply to all ages.**


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**Autoimmune Dysautonomia Evaluation, Serum**

**Clinical Information:** Autoimmune dysautonomia encompasses disorders of peripheral autonomic synapses, ganglionic neurons, autonomic nerve fibers, and central autonomic pathways mediated by neural-specific IgG or effector T cells. These disorders may be idiopathic or paraneoplastic, subacute or insidious in onset, and may present as a limited disorder or generalized pandysautonomia. Pandysautonomia is usually subacute in onset and severe, and includes impaired pupillary light reflex, anhidrosis, orthostatic hypotension, cardiac arrhythmias, gastrointestinal dysmotility, sicca manifestations, and bladder dysfunction. Limited dysautonomia is confined to 1 or just a few domains, is often mild and may include sicca manifestations, postural orthostatism and cardiac arrhythmias, bladder dysfunction, or gastrointestinal dysmotilities. Diagnosis of limited dysautonomia requires documentation of objective abnormalities by autonomic reflex testing, thermoregulatory sweat test, or gastrointestinal motility studies. The most commonly encountered autoantibody marker of autoimmune dysautonomia is the neuronal ganglionic alpha-3-(acetylcholine receptor: AChR) autoantibody. This autoantibody to date is the only proven effector of autoimmune dysautonomia. A direct relationship has been demonstrated between antibody titer and severity of dysautonomia in both alpha-3-AChR-immunized animals and patients with autoimmune dysautonomia. Patients with high alpha-3-AChR autoantibody values (>1.0 nmol/L) generally have profound pandysautonomia. Dysautonomic patients with lower alpha-3-AChR autoantibody values (0.03-0.99 nmol/L) have limited dysautonomia. Importantly, cancer is detected in 30% of patients with alpha-3-AChR autoantibody. Cancers recognized most commonly include small-cell lung carcinomas, thymoma, adenocarcinomas of breast, lung, prostate, and gastrointestinal tract, and lymphoma. Cancer risk factors include a past or family history of cancer, history of smoking, or social or environmental exposure to carcinogens. Early diagnosis and treatment of the neoplasm favors neurologic improvement and lessens morbidity. Autoantibodies to other onconeural proteins shared by neurons, glia or muscle (eg, antineuronal nuclear antibody-type 1: ANNA-1, CRMP-5-IgG, N-type voltage-gated calcium channel, muscle AChR, and sarcomeric [striational antigens]) serve as additional markers of paraneoplastic or idiopathic dysautonomia. A specific neoplasm is often predictable by the individual patient's autoantibody profile.

**Useful For:** Investigating idiopathic dysautonomic symptoms Directing a focused search for cancer in patients with idiopathic dysautonomia Investigating autonomic symptoms that appear in the course or wake of cancer therapy and are not explainable by recurrent cancer or metastasis (detection of autoantibodies in this profile helps differentiate autoimmune dysautonomia from the effects of chemotherapy)

**Interpretation:** Antibodies directed at onconeural proteins shared by neurons, muscle, and glia are valuable serological markers of a patient's immune response to cancer. These autoantibodies are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. It is not uncommon for more than 1 autoantibody to be detected in patients with autoimmune dysautonomia. These include: -Plasma membrane cation channel antibodies (neuronal ganglionic [alpha-3] and muscle [alpha-1] acetylcholine receptor; neuronal calcium channel N-type or P/Q-type, and neuronal voltage-gated potassium channel antibodies). All of these autoantibodies are potential effectors of autonomic dysfunction. -Antineuronal nuclear autoantibody-type 1 -Neuronal and muscle
cytoplasmic antibodies (CRMP-5 IgG, glutamic acid decarboxylase and striational) A rising autoantibody titer in previously seropositive patients suggests cancer recurrence.

**Reference Values:**

**CATION CHANNEL ANTIBODIES**
- N-Type Calcium Channel Antibody
  - < or =0.03 nmol/L
- P/Q-Type Calcium Channel Antibody
  - < or =0.02 nmol/L
- AChR Ganglionic Neuronal Antibody
  - < or =0.02 nmol/L
- Neuronal VGKC Autoantibody
  - < or =0.02 nmol/L
- Glutamic Acid Decarboxylase (GAD65) Antibody
  - < or =0.02 nmol/L

**NEURONAL NUCLEAR ANTIBODIES**
- Antineuronal Nuclear Antibody-Type 1 (ANNA-1)
  - <1:240
- Antineuronal Nuclear Antibody-Type 2 (ANNA-2)
  - <1:240
- Antineuronal Nuclear Antibody-Type 3 (ANNA-3)
  - <1:240
- Anti-Glial/Neuronal Nuclear Antibody-Type 1 (AGNA-1)
  - <1:240

**NEURONAL AND MUSCLE CYTOPLASMIC ANTIBODIES**
- Purkinje Cell Cytoplasmic Antibody, Type 1 (PCA-1)
  - <1:240
- Purkinje Cell Cytoplasmic Antibody, Type 2 (PCA-2)
  - <1:240
- Purkinje Cell Cytoplasmic Antibody, Type Tr (PCA-Tr)
  - <1:240
- Amphiphysin Antibody
  - <1:240
- CRMP-5-IgG
  - <1:240

Note: Titers lower than 1:240 are detectable by recombinant CRMP-5 Western blot analysis. CRMP-5 Western blot analysis will be done on request on stored serum (held 4 weeks). This supplemental testing is recommended in cases of chorea, vision loss, cranial neuropathy, and myelopathy. Call the Neuroimmunology Laboratory at 800-533-1710 or 507-266-5700 to request CRMP-5 Western blot.

- Striational (Striated Muscle) Antibodies
  - <1:120

**ACHR RECEPTOR ANTIBODIES**
- ACh Receptor (Muscle) Binding Antibody
  - < or =0.02 nmol/L
- AChR Receptor (Muscle) Modulating Antibody
  - 0-20% loss of AChR

- Neuromyelitis Optica (NMO)/Aquaporin-4-IgG FACS Assay
  - Negative

- Paraneoplastic Western Blot
  - Negative
- CRMP-5-IgG Western Blot
  - Negative
Amphiphysin Western Blot
Negative

N-Methyl-D-aspartate receptor (NMDA-R)
CBA: Negative
IFA: <1:120

2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid receptor (AMPA-R)
CBA: Negative
IFA: <1:120

Gamma-Amino Butyric acid-type B receptor (GABA-B-R)
CBA: Negative
IFA: <1:120

Leucine-Rich Glioma Inactivated Protein-1 IgG (LGI1)
Negative

Contactin-Associated Protein-Like-2 IgG (CASPR2)
Negative


Autoimmune Gastrointestinal Dysmotility Evaluation, Serum

Clinical Information: Autoimmune gastrointestinal dysmotility (AGID) is a limited form of dysautonomia (also known as autoimmune autonomic ganglionopathy or neuropathy) that is sometimes a paraneoplastic disorder. Neoplasms most commonly found are lung cancer, thymoma, and miscellaneous adenocarcinomas. Diagnosis is confirmed by objective abnormalities on gastrointestinal (GI) motility studies (eg, gastric, small intestinal or colonic nuclear transit studies; esophageal, gastroduodenal, or colonic manometry or anorectal manometry with balloon expulsion). These disorders target autonomic postganglionic synaptic membranes and in some cases ganglionic neurons and autonomic nerve fibers, and may be accompanied by sensory small fiber neuropathy. Onset may be subacute or insidious. There may be additional manifestations of dysautonomia (eg, impaired pupillary light reflex, anhidrosis, orthostatic hypotension, sicca manifestations, and bladder dysfunction) or signs of other neurologic impairment. Autonomic reflex testing and a thermoregulatory sweat test are valuable aids in documentation of objective abnormalities. The serological profile of AGID may include autoantibodies specific for onconeural proteins found in the nucleus, cytoplasm, or plasma membrane of neurons or muscle. Some of these autoantibodies are highly predictive of an underlying cancer. A commonly encountered autoantibody marker of AGID is the ganglionic neuronal alpha-3-AChR (acetylcholine receptor) autoantibody. The pathogenicity of this autoantibody was demonstrated in rabbits immunized with a recombinant extracellular fragment of the alpha-3-AChR subunit, and in mice injected with IgG from high-titered alpha-3-AChR autoantibody-positive rabbit or human sera. A direct relationship between antibody titer and severity of dysautonomia occurs in both experimental animals and patients. Patients with high alpha-3-AChR autoantibody values (>1.0 nmol/L) generally present with profound pandysautonomia, and those with lower alpha-3-AChR autoantibody values may have limited autoimmune dysautonomia, or other neurological symptoms and signs. Importantly, cancer is detected in 30% of patients with alpha-3-AChR autoantibody. Cancer risk factors include the patient's past or family history of cancer, history of smoking, or social and environmental exposure to carcinogens. Early diagnosis and treatment of the neoplasm favors less morbidity from the GI dysmotility disorder. The cancers recognized most commonly with alpha-3-AChR autoantibody include adenocarcinomas of breast, lung, prostate, and GI tract, or lymphoma. A specific neoplasm is often predictable when a patient's autoantibody profile includes other autoantibodies to onconeural proteins shared by neurons, glia, or muscle. Small-cell lung carcinoma is found in 80% of antineuronal nuclear
antibody-type 1 (ANNA-1) (anti-Hu)-positive patients and 23% of ANNA-1-positive patients have GI dysmotility. The most common GI manifestation is gastroparesis, but the most dramatic is pseudoobstruction.

**Useful For:** Investigating unexplained weight loss, early satiety, anorexia, nausea, vomiting, constipation or diarrhea in a patient with past or family history of cancer or autoimmunity. Directing a focused search for cancer. Investigating gastrointestinal symptoms that appear in the course or wake of cancer therapy, not explainable by recurrent cancer, metastasis or therapy; detection of autoantibodies on this profile helps differentiate autoimmune gastrointestinal dysmotility from the effects of chemotherapy. Detecting early evidence of cancer recurrence in previously seropositive patients who have a rising titer of 1 or more autoantibodies.

**Interpretation:** Antibodies directed at onconeural proteins shared by neurons, muscle, and certain cancers are valuable serological markers of a patient's immune response to cancer. They are not found in healthy subjects, and are usually accompanied by subacute symptoms and signs. It is not uncommon for more than 1 antibody to be detected. Three classes of antibodies are recognized (the individual antibodies from each class included in the profile are denoted in parentheses): -Antineuronal nuclear autoantibody-type 1 -Neuronal and muscle cytoplasmic (CRMP-5, glutamic acid decarboxylase, and striational) -Plasma membrane cation channel (neuronal ganglionic [alpha-3-AChR (acetylcholine receptor)] and muscle AChR, neuronal voltage-gated N-type calcium channel, neuronal voltage-gated potassium channel antibodies). All of these autoantibodies are potential effectors of autoimmune gastrointestinal dysmotility.

**Reference Values:**

**NEURONAL NUCLEAR ANTIBODIES**
- Antineuronal Nuclear Ab, Type 1 (ANNA-1) <1:240
- Antineuronal Nuclear Ab, Type 2 (ANNA-2) <1:240
- Antineuronal Nuclear Ab, Type 3 (ANNA-3) <1:240
- Anti-Glial/Neuronal Nuclear Ab, Type 1 (AGNA-1) <1:240

**NEURONAL AND MUSCLE CYTOPLASMIC ANTIBODIES**
- Purkinje Cell Cytoplasmic Ab, Type 1 (PCA-1) <1:240
- Purkinje Cell Cytoplasmic Ab, Type 2 (PCA-2) <1:240
- Purkinje Cell Cytoplasmic Ab, Type Tr (PCA-Tr) <1:240
- Amphiphysin Antibody <1:240
- CRMP-5-IgG <1:240
- Striational (Striated Muscle) Antibodies <1:120

**WESTERN BLOT**
- Paraneoplastic Western Blot Negative
- CRMP-5-IgG Western Blot Negative
- Amphiphysin Western Blot Negative

**ISLET CELL ANTIBODIES**
- Glutamic Acid Decarboxylase (GAD65) Antibody
< or =0.02 nmol/L

**CATION CHANNEL ANTIBODIES**

N-Type Calcium Channel Antibody  
< or =0.03 nmol/L

P/Q-Type Calcium Channel Antibody  
< or =0.02 nmol/L

AChR Ganglionic Neuronal Antibody  
< or =0.02 nmol/L

Neuronal VGKC Autoantibody  
< or =0.02 nmol/L

**ACHR RECEPTOR ANTIBODIES**

ACh Receptor (Muscle) Binding Antibody  
< or =0.02 nmol/L

AChR Receptor (Muscle) Modulating Antibody  
0-20% loss of AChR

N-Methyl-D-aspartate receptor (NMDA-R)  
CBA: Negative

IFAX: <1:120

2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid receptor (AMPA-R)  
CBA: Negative

IFAX: <1:120

Gamma-Amino Butyric acid-type B receptor (GABA-B-R)  
CBA: Negative

IFAX: <1:120

Leucine-Rich Glioma Inactivated Protein-1 IgG (LGI1)  
Negative

Contactin-Associated Protein-Like-2 IgG (CASPR2)  
Negative

Neuromyelitis Optica (NMO)/Aquaporin-4-IgG FACS Assay  
Negative

**Clinical References:**


**ALDP 33743**

**Autoimmune Liver Disease Panel, Serum**

**Clinical Information:** Autoimmune liver diseases result from damage to hepatocytes or cholangiocytes caused by an inflammatory immune reaction. Included within this disease group are autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC). In some cases, patients with these diseases may present asymptomatically, with increases in various liver enzymes being identified incidentally during an unrelated clinical evaluation. On the other end of the spectrum are patients who present with clinical evidence of liver disease, including fatigue,
hepatomegaly, ascites, esophageal varices, and/or jaundice. Diagnosis of an autoimmune liver disease first requires that other etiologies of liver injury, including viral, drug, and metabolic causes, be excluded. In some situations, a liver biopsy may be indicated. For those patients in whom an autoimmune liver disease is suspected, autoantibody serology testing may be considered. The Autoimmune Liver Disease Panel, S includes markers that may support a diagnosis of an autoimmune liver disease, specifically AIH or PBC. Unfortunately, there are no known autoantibodies specific for PSC that are useful as diagnostic markers. Patients with AIH may be positive for smooth muscle antibodies (SMAs) and/or antinuclear antibodies (ANAs). The SMAs associated with AIH are generally specific for F-actin. SMAs have a specificity of 80% to 90% for AIH, although the sensitivity is only in the range of 70% to 80%. In contrast, ANAs, although relatively sensitive for AIH, lack specificity, being associated with a variety of autoimmune diseases. Both SMA and ANA, along with other lab markers and biopsy evaluation, are included in the international diagnostic criteria for AIH. Anti-mitochondrial antibodies (AMAs) are a diagnostic marker for PBC. AMAs are found in >90% of patients with PBC, with a specificity of >95%. AMAs are included in the diagnostic criteria for PBC, which was developed through an international collaborative effort.

**Useful For:** Evaluation of patients with suspected autoimmune liver disease, specifically autoimmune hepatitis or primary biliary cirrhosis. Evaluation of patients with liver disease of unknown etiology.

**Interpretation:** The presence of smooth muscle antibodies (SMAs) and/or antinuclear antibodies (ANAs) is consistent with a diagnosis of chronic autoimmune hepatitis, in patients with clinical and/or laboratory evidence of hepatocellular damage. The presence of anti-mitochondrial antibodies (AMAs) is consistent with a diagnosis of primary biliary cirrhosis, in patients with clinical and/or laboratory evidence of hepatobiliary damage.

**Reference Values:**

**SMOOTH MUSCLE ANTIBODIES**

- **Negative**
- If positive, results are titered.
- Reference values apply to all ages

**MITOCHONDRIAL ANTIBODIES (M2)**

- **Negative:** <0.1 Units
- **Borderline:** 0.1-0.3 Units
- **Weakly positive:** 0.4-0.9 Units
- **Positive:** > or =1.0 Units
- Reference values apply to all ages.

**ANTINUCLEAR ANTIBODIES (ANA2)**

- **Negative:** < or =1.0 Units
- **Weakly positive:** 1.1-2.9 Units
- **Positive:** 3.0-5.9 Units
- **Strongly positive:** > or =6.0 Units
- Reference values apply to all ages.

inflammatory lesions are non-neoplastic and sterile. While periodic fever adenitis pharyngitis aphthous ulcer (PFAPA) syndrome (aphthous stomatitis, pharyngitis, and adenitis), systemic juvenile idiopathic arthritis (sJIA), adult-onset Still disease, and Behcet disease overlap phenotypically with autoinflammatory conditions, a genetic cause of these disorders has not been identified and, therefore, they are not included on this panel. Several of the autoinflammatory conditions represented on this panel are responsive to IL-1 blocking therapies; therefore, determining the underlying genetic cause may help guide treatment decisions. Monogenic autoinflammatory conditions include the periodic fever syndromes (ie, familial Mediterranean fever, cryopyrinopathy-associated periodic syndrome, Muckle-Wells syndrome, familial cold autoinflammatory syndrome, neonatal onset multisystem inflammatory disease or chronic infantile neurologic cutaneous and articular syndrome, tumor necrosis factor [TNF] receptor-associated periodic syndrome, hyper IgD syndrome/Mevalonate kinase deficiency), diseases with pyogenic lesions (ie, deficiency of IL-1 receptor antagonist [DIRA]; pyogenic arthritis, pyoderma gangrenosum and acne [PAPA]; Majeed syndrome), diseases with granulomatous lesions (ie, Blau syndrome), diseases with psoriasis (ie, deficiency of interleukin 36 receptor antagonist [DITRA]); diseases with panniculitis-induced lipodystrophy (JMP syndrome, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome [CANDLE], Nakajo-Nishimura syndrome [NNS], proteasome-associated autoinflammatory syndromes [PRAAS]), DITRA and CARD14-mediated psoriasis (CAMS) both present with pustular skin lesions and early-onset inflammatory bowel disease (IBD). See Table 1 for a summary of genes included in this panel, associated diseases, and the mode of inheritance. NOD2-associated autoinflammatory disease (NAID), also known as Yao syndrome, is a newly-described clinical entity characterized by recurrent fever, dermatitis, and inflammatory arthritis along with GI symptoms in a majority of the patients. Variants in NOD2 have been associated with NAID; however, the variants that have been implicated to date are common variants that confer risk for development of the disorder and are not diagnostic. These common variants are not included in the report for this panel; however, a list of all common variants identified is available by request. While several of the autoinflammatory conditions, including those without a known genetic basis, are responsive to interleukin-1 (IL-1) blocking therapies, PRAAS, CANDLE, DITRA, and CAMPS are not responsive to IL-1 blockade. Anakinra, Rilonacept, and Canakinumab are several examples of medications that target IL-1. The NOD-like receptors (NLRs), which include 23 family members in humans, are an integral part of the innate immune system. NLRs are involved in the formation of the inflammasome, of which the NLRP3 (NALP3) inflammasome is most relevant to human disease and is responsible for activation of the proinflammatory cytokine IL-1 beta. Table 1. Genes included in the Autoinflammatory Gene Panel (listed in alphabetical order) GENE SYMBOL (ALIAS) PROTEIN OMIM INCIDENT INHERITANCE PHENOTYPE DISORDER CARD14 Caspase recruitment domain-containing protein 14 isoform 1 607211 Rare AD Pityriasis rubra pilaris, psoriasis 2 (CAMS) IL10RA Interleukin-10 receptor subunit alpha precursor 146933 Rare AR Very early onset inflammatory bowel disease 28 (VEOIBD) IL10RB Interleukin-10 receptor subunit beta precursor 123889 Rare AR Very early onset inflammatory bowel disease 25 (VEOIBD) IL1RN Interleukin-1 receptor antagonist protein isoform 2 147679 Rare AR Deficiency of interleukin 1 receptor antagonist (DIRA) 1L36RN Interleukin-36 receptor antagonist protein 605507 Rare AR Pustular psoriasis 14, deficiency of IL36 receptor antagonist (DITRA) ISG15 Ubiquitin-like protein ISG15 precursor 147571 Rare AR Immunodeficiency 38 LPIN2 Phosphatidate phosphatase LPIN2 605519 Primarily identified in Arab ethnicities AR Majeed syndrome MEFV Pyrin isoform 1 608107 Primarily identified in Armenian, Arab, Turkish, Italian, and Jewish ethnicities AR(most), AD(rarely) Familial Mediterranean fever (FMF) MVK Mevalonate kinase isoform a 251170 Primarily identified in Caucasians of western European ancestry AR / AD Hyperimmunoglobulinemia D syndrome (HIDS), Mevalonate kinase-associated periodic fever syndrome, Mevalonic aciduria, Porokeratosis 3, multiple types (AD) NLRP12 (NALP12) NACHT, leucine rich repeat (LRR) and PYD domains-containing protein 12 isoform 2 609648 Rare AR Familial cold autoinflammatory syndrome 2 (FCAS2) NLRP3 (NALP3) (CIAS1) NACHT, LRR and PYD domains-containing protein 3 isoform 1 606416 Primarily identified in Caucasians of western European ancestry AD Familial cold autoinflammatory syndrome 1 (FCAS1), Muckle-Wells syndrome; Neonatal onset multisystem inflammatory disease (NOMID)/chronic infantile neurological cutaneous and articular syndrome (CINCA) NOD2 (CARD15) Nucleotide-binding oligomerization domain-containing protein 2 isoform 1 605956 Rare AD Blau syndrome, Early-onset Sarcoidosis, Inflammatory bowel disease 1 Pediatric granulomatous arthritis (PGA) PLCG2 1-Phosphatidylinositol 4,5-bisphosphate phosphodiesterase gamma-2 600220 Rare AD PLC gamma 2-associated antibody deficiency and immune dysregulation (PLAID), autoinflammation and PLC gamma 2-associated antibody deficiency and immune dysregulation (APLAID) PSMB8 Proteasome subunit beta type-8 isoform E2 precursor 177046 Rare AR
CANDLE (chronic atypical neutrophilic dermatitis with lipodystrophy); JMP (joint contractures, muscular atrophy, microcytic anemia, and panniculitis-induced lipodystrophy); PRASS (proteasome-associated auto-inflammatory syndrome); JASL (Japanese autoinflammatory syndrome with lipodystrophy) PSTPIP1 (CD2BP1) Proline-serine-threonine phosphatase-interacting protein 1 606347 Rare AD Pyogenic sterile arthritis pyoderma gangrenosum acne (PAPA) RBCK1 (HOIL1) RanBP-type and C3HC4-type zinc finger-containing protein 1 isoform 2 610924 Rare AR Polyglucosan body myopathy 1 with or without immunodeficiency; chronic autoinflammation, invasive bacterial infections, muscle amylopectinosis SH3BP2 SH3 domain-binding protein 2 isoform a 602104 Rare AD Cherubism, autoinflammatory bone disease TNFRSF1A Tumor necrosis factor receptor superfamily member 1A precursor 191190 Primarily identified in Caucasians of western European ancestry AD Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) AD=autosomal dominant AR=autosomal recessive XL=X-linked

**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of autoinflammatory syndromes and related disorders Establishing a diagnosis of autoinflammatory disease, and in some cases guiding management and allowing for surveillance of disease features Identification of pathogenic variants within genes known to be associated with autoinflammatory disorders allowing for predictive testing of at-risk family members

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

### ARPKZ

**Autosomal Recessive Polycystic Kidney Disease (ARPKD), Full Gene Analysis**

**Clinical Information:** Autosomal recessive polycystic kidney disease (ARPKD) is a disorder caused by mutations in the polycystic kidney and hepatic disease 1 (PKHD1) gene. The incidence of ARPKD is approximately 1:20,000 and the estimated carrier frequency in the general population is 1:70. ARPKD is characterized by enlarged echogenic kidneys, congenital hepatic fibrosis, and pulmonary hypoplasia (secondary to oligohydramnios [insufficient volume of amniotic fluid] in utero). Most individuals with ARPKD present during the neonatal period and, of those, nearly one-third die of respiratory insufficiency. Early diagnosis, in addition to initiation of renal replacement therapy (dialysis or transplantation) and respiratory support, increases the 10-year survival rate significantly. Presenting symptoms include bilateral palpable flank masses in infants and subsequent observation of typical findings on renal
ultrasound, often within the clinical context of hypertension and prenatal oligohydramnios. In rarer cases, individuals may present during childhood or adulthood with hepatosplenomegaly. Of those who survive the neonatal period, one-third progress to end-stage renal disease and up to one-half develop chronic renal insufficiency. The PKHD1 gene maps to 6p12 and includes 67 exons. The PKHD1 gene encodes a protein called fibrocystin, which is localized to the primary cilia and basal body of renal tubular and biliary epithelial cells. Because ARPKD is an autosomal recessive disease, affected individuals must carry 2 deleterious mutations within the PKHD1 gene. Although disease penetrance is 100%, intrafamilial variation in disease severity has been observed. Mutation detection is often difficult due to the large gene size and the prevalence of private mutations that span the entire length of the gene.

Useful For:
- Diagnosis of individuals suspected of having autosomal recessive polycystic kidney disease (ARPKD)
- Prenatal diagnosis if there is a high suspicion of ARPKD based on ultrasound findings
- Carrier testing of individuals with a family history of ARPKD but an affected individual is not available for testing or disease-causing mutations have not been identified

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

Avocado IgG
Interpretation: mcg/mL of IgG
Lower Limit of Quantitation: 2.0
Upper Limit of Quantitation: 200

Reference Values:
< 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Avocado, IgE
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and
wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**AXIN2 Gene, Full Gene Analysis**

**Clinical Information:** Oligodontia, defined as the congenital absence of 6 or more permanent teeth, can occur as either an isolated finding or as part of an underlying syndrome. AXIN2 is one of several genes that have been associated with nonsyndromic oligodontia. In a subset of patients, mutations in the AXIN2 gene have been found to be associated with a combined oligodontia-colorectal cancer syndrome. Oligodontia-colorectal cancer syndrome is a rare hereditary cancer syndrome. One study of a Finnish family with AXIN2-related oligodontia-colorectal cancer syndrome identified colorectal cancer in 67% (6 of 9) of family members with oligodontia and a confirmed AXIN2 mutation. The AXIN2 mutation in this family was inherited in an autosomal dominant fashion. In the same study, a de novo AXIN2 mutation was identified in a 13-year-old patient with oligodontia but no history of colorectal cancer. Somatic AXIN2 mutations have been identified in mismatch repair-deficient colorectal tumors and have been shown to cause accumulation of beta-catenin and subsequent activation of T-cell factor-dependent transcription. These findings support the role of AXIN2 in tumorigenesis.

**Useful For:** Confirmation of oligodontia-colorectal cancer syndrome in patients with clinical features

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity, and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.

**Azathioprine (Imuran) as 6-Mercaptopurine**

**Reference Values:**

Units: ng/mL

Azathioprine is measured as the metabolite, 6-mercaptopurine. Therapeutic and toxic ranges have not been established. Usual therapeutic doses produce 6-mercaptopurine serum concentrations of less than 1000 ng/ml.

**B-Cell CD40 Expression by Flow Cytometry, Blood**

**Clinical Information:** The adaptive immune response includes both cell-mediated (mediated by T cells and natural killer [NK] cells) and humoral (mediated by B cells) immunity. After antigen recognition and maturation in secondary lymphoid organs, some antigen-specific B cells terminally differentiate into antibody-secreting plasma cells. Decreased numbers or aberrant function of B cells result in humoral immune deficiency states with increased susceptibility to infections, and these may be either primary (genetic) or secondary immunodeficiencies. Secondary causes include medications, malignancies, infections, and autoimmune disorders (this does not cause immunodeficiency with increased infection). CD40 is a member of the tumor necrosis factor receptor superfamily, expressed on a wide range of cell types including B cells, macrophages, and dendritic cells. CD40 is the receptor for CD40 ligand (CD40LG), a molecule predominantly expressed by activated CD4+ T cells. CD40/CD40LG interaction is involved in the formation of memory B lymphocytes and promotes immunoglobulin (Ig) isotype switching. CD40LG expression in T cells requires cellular activation, while CD40 is constitutively expressed on the surface of B cells and other antigen-presenting cells. Hyperimmunoglobulin M (hyper-IgM or HIGM) syndrome is a rare primary immunodeficiency characterized by increased or normal levels of IgM with low IgG and/or IgA. (2) Patients with hyper-IgM syndromes may have genetic defects or mutations in 1 of several known genes. Some of these genes are CD40LG, CD40, AICDA (activation-induced cytidine deaminase), UNG (uracil DNA glycosylase), and IKBKG (inhibitor of kappa light polypeptide gene enhancer in B cells, kinase gamma; also known as NEMO). (2) Not all cases of hyper-IgM syndrome fit into these known genetic defects. Mutations in CD40LG and IKBKG are inherited in an X-linked fashion, while mutations in the other 3 genes are autosomal recessive. Elevated IgM is only one of the features of NEMO deficiency and therefore, it is no longer classified exclusively with the hyper-IgM syndromes. Distinguishing between the different forms of hyper-IgM syndrome is very important because of differing prognoses. CD40 and CD40LG deficiency are among the more severe forms, which typically manifest in infancy or early childhood, and are characterized by an increased susceptibility to opportunistic pathogens (e.g., Pneumocystis carinii, Cryptosporidium, and Toxoplasma gondii). (3) CD40 deficiency, also known as hyper-IgM type 3 (HIGM3), accounts for <1% of hyper-IgM syndromes. Flow cytometry analysis shows complete lack of CD40 expression on the B cells of these patients. (4) Intravenous injection with IgG is the treatment of choice along with immune reconstitution with hematopoietic cell transplantation. To date, all documented CD40-deficient patients have been diagnosed before age 1. Consequently, when used in the context of HIGM3, this test is only indicated in children (for diagnosis). In the case of CD40L deficiency, this test can be used for male patients or in females of child-bearing age (to identify carriers). A larger age spectrum has been reported with CD40L deficiency, ranging from infancy to
early adulthood. CD40 expression on B cells is also an indicator of immune status (eg, after the use of biological immunomodulatory therapy for autoimmune disease, cancer and transplantation).

**Useful For:** Evaluating patients for hyper-IgM type 3 (HIGM3) syndrome due to defects in CD40, typically seen in patients <10 years of age Assessing B-cell immune competence in other clinical contexts, including autoimmunity, malignancy and transplantation

**Interpretation:** This assay is qualitative; CD40 expression is reported as present (normal) or absent (abnormal). Normal B cells express surface CD40 on the majority of cells. Hyper-IgM (HIGM3) syndrome patients typically do not express CD40 on the surface of B cells. Genotyping of CD40 is required for a definite diagnosis of HIGM3. Call 800-533-1710 for ordering assistance.

**Reference Values:**
Present (normal)

**Clinical References:**

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**BCLGP 65664**

**B-Cell Deficiency Primary Immunodeficiency (PID) Gene Panel**

**Clinical Information:** Primary B-cell disorders/humoral immunodeficiencies are characterized by an insufficient number of B-cells or impaired functioning/differentiation of B-cells. B-cell disorders account for approximately two-thirds of all genetic primary immunodeficiencies (PID) and may result in decrease or dysfunction of one or more isotypes of immunoglobulin, leading to increased susceptibility to infection, particularly bacterial infections such as sinopulmonary infections, gastrointestinal infections, otitis, skin infections, and conjunctivitis. In the absence of infection, patients may be asymptomatic and, thus, difficult to diagnose. In addition, primary B-cell disorders may result in lymphoproliferative disorders or be associated with autoimmune (AI) manifestations, including AI cytopenias, AI endocrine disorders and AI enteropathy among others. There are several PID that also have an associated T-cell and/or other cellular immunodeficiency, in addition to the B-cell defects. In some disorders with agammaglobulinemia or hypogammaglobulinemia, patients may have reduced numbers of B-cells, resulting in a severe reduction in all antibody isotypes. Often, they present in the first few years of life with recurrent bacterial infections, a severe life-threatening bacterial infection (ie, meningitis, sepsis), and decreased lymphoid tissue (ie, small adenoids, tonsils, and lymph nodes in X-linked agammaglobulinemia, due to Bruton tyrosine kinase [BTK] gene mutations). Inheritance can be either X-linked (eg, due to variants in BTK), or autosomal recessive (eg, IGHM, CD79A, CD79B, IGLL1, BLNK, LRRC8A, and PIK3R1). B-cell lymphopenia with hypogammaglobulinemia can also be observed in WHIM syndrome (warts, hypogammaglobulinemia, infections, and myelokathexis), which results from pathogenic gain-of-function variants in the CXCR4 gene. These patients also have severe peripheral neutropenia (ANC<500) with evidence of myelokathexis (neutrophil retention) in the bone marrow. In addition to recurrent infections (sinopulmonary, urinary tract, otitis media, deep soft tissue abscesses, skin), patients are also susceptible to warts and condyloma acuminata due to human papillomavirus (HPV) infection. Common variable immunodeficiency (CVID) is the most common adult humoral immunodeficiency with an incidence of approximately 1:25,000 to 1:50,000. CVID may present with frequent and unusual infections during early childhood, adolescence, or adulthood. As per current diagnostic criteria, CVID is not considered in children younger than 4 years of age. In addition, a significant proportion of patients may have autoimmune or inflammatory manifestations, enlarged lymphoid tissues, granulomas, and an increased susceptibility to cancer. These patients typically have normal numbers of B-cells (<5% of CVID patients have less than 1% of B cells, which are considered to be due to early B cell defects), but have impaired terminal differentiation, resulting in decreased levels of IgG and IgA, with or without a decrease in IgM. Over two-thirds of patients have quantitative defects in switched memory B-cells. Some patients may also have quantitative and functional T-cell defects or NK cell deficiency. Patients with decreased naive T-cell numbers are considered to have late-onset combined
deficiency (LOCID). Genetic variants have been identified in several genes, including ICOS, TNFRSF13B (TAC1), CD19, TNFRSF13C (BAFFR), MS4A1 (CD20), CR2 (CD21), CD81, LRBA, NFKB2, IKZF1 (IKAROS), among others, in a subset of CVID patients. However, the majority of these patients have unknown genetic defects and may have oligogenic or polygenic causes of disease.

Dysgammaglobulinemias including hyper-IgM syndrome and selective antibody deficiencies may also occur where a patient is either lacking a specific immunoglobulin isotype (eg, selective IgA deficiency) or a specific vaccine antibody response (impaired pneumococcal polysaccharide responsiveness) or may have an elevated/normal IgM level. Selective deficiencies (ie, IgA deficiency, IgG deficiency) may be due to mutations in genes encoding immunoglobulin heavy or light chains. Selective IgA deficiency (sIgAD) is the most common PID with an incidence of 1:200 to 1:1000, depending on the cohort studied. Most patients with sIgAD are asymptomatic though some may have frequent infections. There is also a higher incidence of celiac disease in this group. Most patients with selective antibody deficiencies are treated if they have frequent infections in addition to impaired vaccine antibody responses. Some patients with sIgAD may have autoantibodies to IgA. Hyper IgM syndrome (mostly commonly due to variants in CD40LG but also due to other genes, eg, CD40, AICDA, PI3KCD, UNG) is characterized by an inability to switch from the production of IgM-type antibodies to IgG, IgA, or IgE isotypes. These individuals typically have a normal number of B-cells. Patients with CD40L and CD40 deficiency tend to present with severe opportunistic infections more reminiscent of a cellular immunodeficiency and, therefore, may also be considered as combined immunodeficiencies. Primary B-cell disorders may also result in lymphoproliferative diseases characterized by dysgammaglobulinemia/hypogammaglobulinemia, persistent or severe complications of Epstein-Barr virus (including hemophagocytic lymphohistiocytosis), and lymphoproliferative disorders (including malignant lymphomas). Lymphomas that are associated with these disorders are typically high-grade B-cell lymphomas, non-Hodgkin type, extranodal, and often involve the intestine. Inflammatory bowel disease has also been associated with some forms. Inheritance of these lymphoproliferative diseases can be X-linked or autosomal recessive. For example, X-linked lymphoproliferative disease (XLP) is due to pathogenic variants in SH2D1A (XLP-1), while autosomal recessive lymphoproliferative syndrome 2 is caused by pathogenic variants in TNFRSF7, which encodes CD27. Some of these lymphoproliferative disorders clinically manifest following infection, especially with Epstein-Barr virus (EBV). Post-meiotic segregation disorder, due to pathogenic variants in PMS2, leads to defective class switching from IgM and results in low serum IgG and IgA with elevated IgM. Patients also often demonstrate cafe-au-lait macules and are predisposed to several types of malignancy due to Lynch syndrome. PMS2 testing will be performed only for patients who demonstrate defective class switching. Table 1. Genes included in the B-cell Deficiency/Agammaglobulinemia/Lymphoproliferative Primary Immunodeficiency Gene Panel GENE SYMBOL (ALIAS) PROTEIN OMIM INCIDENCE INHERITANCE PHENOTYPE DISORDER AICDA Single-stranded DNA cytosine deaminase 605257 Unknown AR Immunodeficiency with hyper IgM, type 2 BLNK B-cell linker protein isoform 1 1604515 Unknown AR Agammaglobulinemia BTK Tyrosine-protein kinase BTK isoform 1 300300 1-9/million XL X-linked agammaglobulinemia CD79A B-cell antigen receptor complex-associated protein alpha chain isoform 1 precursor 112205 Unknown AR Agammaglobulinemia CD79B (B29) B-cell antigen receptor complex-associated protein beta chain isoform 1 precursor 147245 Unknown AR Agammaglobulinemia CARD11 Caspase recruitment domain-containing protein 11 607210 AR/AD Immunodeficiency 11 (AR), B-cell expansion with NFKB and T-cell anergy (AD) CD19 B-lymphocyte antigen CD19 isoform 2 precursor 107265 Unknown AR Common variable immunodeficiency (CVID) 3 CD27 (TNFRSF7) CD27 antigen precursor 186711 AR Lymphoproliferative syndrome 2 (CD27 deficiency) CD40 Tumor necrosis factor receptor superfamily member 5 isoform 1 precursor 109535 Unknown AR Immunodeficiency with hyper IgM CD40LG CD40 ligand 300386 2/million males XL Immunodeficiency with X-linked hyper IgM CD81 CD81 antigen isoform 1 186845 Unknown AR Common variable immunodeficiency (CVID) 6 CR2 (CD21) Complement receptor type 2 isoform 1 precursor 120650 Unknown AR Common variable immunodeficiency (CVID) 7 CXCR4 C-X-C chemokine receptor type 4 isoform b 162643 AD Myelokathexis, isolated, WHIM syndrome (AD) GATA2 Endothelial transcription factor GATA-2 isoform 1 137295 AD Immunodeficiency 21, Emberger syndrome, susceptibility to acute myeloid Leukemia and myelodysplastic syndrome ICOS Inducible T-cell costimulator precursor 604558 Unknown AR Common variable immunodeficiency (CVID) 1 IGHM IMMUNOGLOBULIN HEAVY CHAIN CONSTANT REGION MU 147020 Unknown AR Agammaglobulinemia 1 IGLL1 (LAMBDA-5) Immunoglobulin lambda-like polypeptide 1 isoform 1 precursor 146770 Unknown AR Agammaglobulinemia IKZF1 (IKAROS) DNA-binding protein Ikaros isoform 2 603023 AD with incomplete penetrance Late-onset B-cell PID LRBA Lipopolysaccharide-responsive and beige-like
anchor protein isoform 2 606453 Unknown AR Common variable immunodeficiency (CVID) 8 with autoimmunity LRRCA8 Volume-regulated anion channel subunit LRRCA8 608360 Unknown AD Agammaglobulinemia MALT1 Mucosa-associated lymphoid tissue lymphoma translocation protein 1 isoform a 604860 AR Immunodeficiency 12 MS4A1 (CD20) B-lymphocyte antigen CD20 112210 AR Common variable immunodeficiency (CVID) 5 NFkB2 Nuclear factor NF-kappa-B p100 subunit isoform a 164012 Unknown AD Common variable immunodeficiency (CVID) 10 PIK3CD Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit delta isoform 602839 Unknown AD Immunodeficiency 14, hyper IgM PIK3R1 Phosphatidylinositol 3-kinase regulatory subunit alpha isoform 1 171833 Unknown AR Agammaglobulinemia PLCG2 1-Phosphatidylinositol 4,5-bisphosphate phosphodiesterase gamma-2 600220 Rare AD Autoinflammation, antibody deficiency, and immune dysregulation syndrome familial cold autoinflammatory syndrome, type III RNF168 E3 ubiquitin-protein ligase RNF168 604907 Unknown AD or AR Common variable immunodeficiency (CVID) 2, immunoglobulin A deficiency TNFRSF13C Tumor necrosis factor receptor superfamily member 13C 606269 Unknown AD or AR Common variable immunodeficiency (CVID) 4 TNFSF12 (TWEAK) Tumor necrosis factor ligand superfamily member 12 proprotein 602695 AD Low IgM and IgA UNG Uracil-DNA glycosylase isoform UNG2 191525 Unknown AR Immunodeficiency with hyper IgM syndrome, type 5 AD autosomal dominant AR autosomal recessive XL=X-linked

**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of primary B-cell deficiencies and related disorders. Patients with B-cell immunodeficiencies who may have other clinical presentations, besides the humoral immune defect, such as inflammatory bowel disease, autoimmunity, or other as indicated above. Establishing a diagnosis of a B-cell deficiency or related disorder, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved. Identifying variants within genes known to be associated with increased risk for disease features allowing for predictive testing of at-risk family members.

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**
ALLM

63052

B-Cell Lymphoblastic Leukemia (B-ALL) Monitoring, Minimal Residual Disease (MRD) Detection, Bone Marrow

Clinical Information: B-cell lymphoblastic leukemia/lymphoma (B-ALL) is a neoplasm of precursor cells (lymphoblasts) committed to B-cell lineage. B-ALL is the most common acute leukemia in children and adolescents, and also occurs in adults. Patients with B-ALL typically present with a high blast count in the peripheral blood, and bone marrow replacement with the disease. The diagnosis of B-ALL is based on a combination of morphologic features showing primarily small blasts with open chromatin and high N:C ratio, and an immunophenotype showing immaturity (CD34 and/or TdT expression) associated with B-cell lineage markers (CD19, CD22, and CD79a). New therapeutic approaches in B-ALL have been increasingly successful. One of the most important predictors of the disease relapse is the ability to detect minimal residual disease (MRD) in the bone marrow specimens following induction phase of the therapy (day 28). Immunophenotyping studies are necessary as morphologic features are not sufficient to detect MRD. The absence of MRD (at 0.01% sensitivity) is an important prognostic indicator in these patients. This test is used to establish an antigen footprint of tumor cells at diagnosis to monitor minimal residual disease in these patients after treatments or transplants.

Useful For: Aids in monitoring a previously confirmed diagnosis of B-cell lymphoblastic leukemia

Interpretation: An interpretive report for the presence or absence of B-cell lymphoblastic leukemia (B-ALL) minimal residual disease (MRD) is provided. Patients who have detectable MRD by this assay are considered to have residual/recurrent B-ALL.

Reference Values: An interpretive report will be provided.

This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and correlation with the morphologic features will be provided by a hematopathologist for every case.

leukemia from normal B precursors with four color flow cytometry: implications for residual disease detection. Leukemia 1999;13:558-567

**B-Cell Lymphoma, FISH, Blood or Bone Marrow**

**Clinical Information:** Lymphoid neoplasms are known to be complex and the prognosis and clinical course of patients with lymphoma is highly variable. Genetic abnormalities have emerged as one of the most reliable criteria for categorizing lymphomas. Several chromosome abnormalities and variants of these abnormalities have been associated with various kinds of lymphoma (see Table). Common Chromosome Abnormalities in B-cell Lymphomas Lymphoma Type Chromosome Abnormality FISH Probe Burkitt (pediatric, ≤18 years old) 8q24.1 rearrangement 5’/3’ MYC t(2;8)(p12;q24.1) IGK/MYC t(8;14)(q24.1;q32) MYC/IGH t(8;22)(q24.1;q11.2) MYC/IGL 3q27 rearrangement 3’/5’ BCL6 18q21 rearrangement 3’/5’ BCL2 Diffuse large B-cell, Burkitt-like "double-hit" 8q24.1 rearrangement 5’/3’ MYC t(8;14)(q24.1;q32) MYC/IGH Reflex: t(2;8)(p12;q24.1) IGK/MYC Reflex: t(8;22)(q24.1;q11.2) MYC/IGL Reflex: 3q27 rearrangement 3’/5’ BCL6 Reflex: 18q21 rearrangement 3’/5’ BCL2 Large BCL with IRF4 Rearranged 6p24.3 rearrangement 3’/5’ IRF4 18q21 rearrangement 3’/5’ BCL2 3q27 rearrangement 3’/5’ BCL2 Follicular 18q21 rearrangement 3’/5’ BCL2 18q21 rearrangement 3’/5’ BCL2 Mantle Cell t(11;14)(q13;q32) CCND1/IGH Blastoid subtype only: deletion of 17p TP53/D17Z1 Blastoid subtype only: 8q24.1 rearrangement 5’/3’ MYC MALT 18q21 deletion 5’/3’ MALT1 Splenic Marginal Zone Deletion of 7q D7Z1/7q32 Deletion of 17p TP53/D17Z1

**Useful For:** Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with various B-cell lymphomas using blood or bone marrow specimens. Tracking known chromosome abnormalities and response to therapy in patients with B-cell neoplasms.

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. Detection of an abnormal clone supports a diagnosis of a B-cell neoplasm; the specific abnormality detected may help subtype the neoplasm. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

**B-Cell Lymphoma, FISH, Tissue**

**Clinical Information:** Mature B-cell lymphoma can be low grade, intermediate grade, or high grade, and the prognosis and clinical course are highly variable. Genetic abnormalities have emerged as one of the most important prognostic markers in B-cell lymphomas and can aid in diagnosis. Several chromosome abnormalities and variants of these abnormalities have been associated with various lymphoma subtypes (see Table). Conventional chromosome studies cannot be employed on paraffin-embedded tissue, and molecular genetic analyses are often problematic in the study of lymphomas. FISH permits the detection of abnormal gene associated with various chromosome translocations and inversions in B-cell lymphoma (see Table). Common Chromosome Abnormalities in B-Cell Lymphomas Lymphoma Type Chromosome Abnormality FISH Probe Burkitt (pediatric, ≤18 years old) 8q24.1 rearrangement 5’/3’ MYC t(2;8)(p12;q24.1) IGK/MYC t(8;14)(q24.1;q32) MYC/IGH
t(8;22)(q24.1;q11.2) MYC/IGL 3q27 rearrangement 3'/5' BCL6 18q21 rearrangement 3'/5' BCL2 Diffuse large B-cell, Burkitt-like "double-hit" 8q24.1 rearrangement 5'/3' MYC t(8;14)(q24.1;q32) MYC/IGH Reflex: t(2;8)(p12;q24.1) IGK/MYC Reflex: t(8;22)(q24.1;q11.2) MYC/IGL Reflex: 3q27 rearrangement 3'/5' BCL6 Reflex: 18q21 rearrangement 3'/5' BCL2 Large BCL with IRF4 Rearranged 6p24.3 rearrangement 3'/5' IFR4 18q21 rearrangement 3'/5' BCL2 3q27 rearrangement 3'/5' BCL6 Follicular 18q21 rearrangement 3'/5' BCL2 3q27 rearrangement 3'/5' BCL6 Mantle Cell t(11;14)(q13;q32) CCND1/IGH Blastoid subtype only: deletion of 17p TP53/D17Z1 Blastoid subtype only: 8q24.1 rearrangement 5'/3' MYC MALT 18q21 rearrangement 5'/3' MALT1 Splenic Marginal Zone Deletion of 7q D7Z1/7q32 Deletion of 17p TP53/D17Z1

**Useful For:** Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with various B-cell lymphomas using tissue specimens Tracking known chromosome abnormalities and response to therapy in patients with B-cell lymphomas

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. Detection of an abnormal clone is supportive of a diagnosis of a B-cell lymphoma. The specific abnormality detected may help subtype the neoplasm. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:** WHO Classification of Tumour of Haematopoietic and Lymphoid Tissues. Edited by SH Swerdlow, E Campo, NL Harris. IARC, Lyon 2008, pp 214-217, 220-226, 229-237, 262-278

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**B-Cell Phenotyping Profile for Immunodeficiency and Immune Competence Assessment, Blood**

**Clinical Information:** Quantitative Lymphocyte Subsets: T, B, and NK: Normal immunity requires a balance between the activities of various lymphocyte subpopulations with different effector and regulatory functions. Different immune cells can be characterized by unique surface membrane antigens described by a cluster of differentiation nomenclature (eg, CD3 is an antigen found on the surface of T lymphocytes). Abnormalities in the number and percent of T (CD3, CD4, CD8), B (CD19), and natural killer (CD16+CD56) lymphocytes have been described in a number of different diseases. In patients who are infected with HIV, the CD4 count is measured for AIDS diagnosis and for initiation of antiviral therapy. The progressive loss of CD4 T lymphocytes in patients infected with HIV is associated with increased infections and complications. The US Public Health Service has recommended that all HIV-positive patients be tested every 3 to 6 months for the level of CD4 T lymphocytes. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon, with no change between noon and afternoon. Natural killer (NK) cell counts, on the other hand, are constant throughout the day.(1) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(2-4) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(2) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening,(5) and during summer compared to winter.(6) These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets. Immune Assessment B Cell Subsets, Blood: The adaptive immune response includes both cell-mediated (mediated by T cells and natural killer: NK cells) and humoral immunity (mediated by B cells). After antigen recognition and maturation in secondary lymphoid organs, some antigen-specific B cells terminally differentiate into antibody-secreting plasma cells or become memory B cells. Memory B cells are 3 subsets: marginal zone B cells (MZ or nonswitched memory), class-switched memory B cells, and IgM-only memory B cells. Decreased B-cell numbers, B-cell function, or both, result in immune deficiency states and increased susceptibility to infections. These decreases may be either...
primary (genetic) or secondary. Secondary causes include medications, malignancies, infections, and autoimmune disorders. Common variable immunodeficiency (CVID), a disorder of B-cell function, is the most prevalent primary immunodeficiency with a prevalence of 1 to 25,000 to 1 to 50,000.(1) CVID has a bimodal presentation with a subset of patients presenting in early childhood and a second set presenting between 15 and 40 years of age, or occasionally even later. Four different genetic defects have been associated with CVID including mutations in the ICOS, CD19, BAFF-R, and TACI genes. The first 3 genetic defects account for approximately 1% to 2%, and TACI mutations account for 8% to 15% of CVID cases. CVID is characterized by hypogammaglobulinemia usually involving most or all of the Ig classes (IgG, IgA, IgM, and IgE), impaired functional antibody responses, and recurrent sinopulmonary infections.(1,2) B-cell numbers may be normal or decreased. A minority of CVID patients (5%-10%) have very low B-cell counts (<1% of peripheral blood leukocytes), while another subset (5%-10%) exhibit noncaseating, sarcoid-like granulomas in different organs and also tend to develop a progressive T-cell deficiency.(1) Of all patients with CVID, 25% to 30% have increased numbers of CD8 T cells and a reduced CD4 to CD8 ratio (<1). Studies have shown the clinical relevance of classifying CVID patients by assessing B-cell subsets, since changes in different B-cell subsets are associated with particular clinical phenotypes or presentations.(3,4) The B-cell phenotyping assay can be used in the diagnosis of hyper-IgM syndromes, which are characterized by increased or normal levels of IgM with low IgG and/or IgA.(5) Patients with hyper-IgM syndromes can have 1 of 5 known genetic defects-mutations in the CD40L, CD40, AID (activation-induced cytidine deaminase), UNG (uracil DNA glycosylase), and NEMO (NF-kappa B essential modulator) genes.(5) Mutations in CD40L and NEMO are inherited in an X-linked fashion, while mutations in the other 3 genes are inherited in an autosomal recessive fashion. Patients with hyper-IgM syndromes have a defect in isotype class-switching, which leads to a decrease in class-switched memory B cells, with or without an increased in nonswitched memory B cells and IgM-only memory B cells. In addition to its utility in the diagnosis of the above-described primary immunodeficiencies, B-cell phenotyping may be used to assess reconstitution of B-cell subsets after hematopoietic stem cell or bone marrow transplant. This test is also used to monitor B-cell-depicting therapies, such as Rituxan (Rituximab) and Zevalin (Ibritumomab tiuxetan). CVID Confirmation Flow Panel: The etiology of CVID is heterogeneous, but recently 4 genetic defects were described that are associated with the CVID phenotype. Specific mutations, all of which are expressed on B cells, have been implicated in the pathogenesis of CVID. These mutations encode for: -ICOS-inducible costimulator expressed on activated T cells(1) -TACI-transmembrane activator and CAML (calcium modulator and cyclophilin ligand) interactor(2) -CD19(3) -BAFF-R-B cell activating factor belonging to the tumor necrosis factor (TNF) receptor family(4) Of these, the TACI mutations probably account for about 10% of all CVID cases.(2) Patients with mutations in the TACI gene are particularly prone to developing autoimmune disease, including cytopenias as well as lymphoproliferative disease. The other mutations each have been reported in only a handful of patients. The etiopathogenesis is still undefined in more than 50% of CVID patients. A BAFF-R defect should be suspected in patients with low to very low class switched and nonswitched memory B cells and very high numbers of transitional B cells (see IABC/87994 B-Cell Phenotyping Screen for Immunodeficiency and Immune Competence Assessment, Blood). Class switching is the process that allows B cells, which possess IgD and IgM on their cell surface as a part of the antigen-binding complex, to produce IgA, IgE, or IgG antibodies. A TACI defect is suspected in patients with low IgM with normal to low switched B cells, with autoimmune and/or lymphoproliferative manifestations, and normal B cell responses to mitogens. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon, with no change between noon and afternoon. Natural killer (NK) cell counts, on the other hand, are constant throughout the day.(5) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(6-8) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(6) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening,(9) and during summer compared to winter.(10) These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

Useful For: Screening for common variable immunodeficiency (CVID) and hyper-IgM syndromes Assessing B-cell subset reconstitution after stem cell or bone marrow transplant Assessing response to
B-cell-depleting immunotherapy Identifying defects in transmembrane activator and calcium modulator and cyclophilin ligand (CAML) interactor (TACI) and B-cell-activating factor receptor (BAFF-R) in patients presenting with clinical symptoms and other laboratory features consistent with CVID

**Interpretation:**

Quantitative Lymphocyte Subsets: T, B, and NK: When the CD4 count falls below 500 cells/mcL, HIV-positive patients can be diagnosed with AIDS and can receive antiretroviral therapy. When the CD4 count falls below 200 cells/mcL, prophylaxis against Pneumocystis jiroveci pneumonia is recommended. Immune Assessment B Cell Subsets, Blood: The assay provides quantitative information on the various B-cell subsets (percentage and absolute counts in cells/microliter). Each specimen is evaluated for B-cell subsets with respect to the total number of CD19+ B cells present in the peripheral blood mononuclear cell population, compared to the reference range. In order to verify that there are no CD19-related defects, CD20 is used as an additional pan-B-cell marker (expressed as percentage of CD45+ lymphocytes). The B-cell panel assesses the following B-cell subsets: -CD19+=B cells expressing CD19 as a percent of total lymphocytes -CD19+ CD27+=total memory B cells -CD19+ CD27+ IgD+ IgM+=marginal zone or nonswitched memory B cells -CD19+ CD27+ IgD- IgM-= IgM-only memory B cells -CD19+ CD27+ IgD- IgM-=class-switched memory B cells -CD19+ IgM+= IgM B cells -CD19+ CD38+ IgM+=transitional B cells -CD19+ CD38+ IgM-=plasmablasts -CD19- CD21+=low (“immature”) B cells -CD19+ CD21+=mature B cells -CD19+ CD20+=B cells co-expressing both CD19 and CD20 as a percent of total lymphocytes For isotype class-switching and memory B-cell analyses, the data will be reported as being consistent or not consistent with a defect in memory and/or class switching. If a defect is present in any of these B-cell subpopulations, further correlation with clinical presentation and additional functional, immunological, and genetic laboratory studies will be suggested. Since each of the 11 B-cell subsets listed above contributes to the diagnosis of common variable immunodeficiency (CVID) and hyper-IgM syndromes and provides further information on the likely specific genetic defect, all the B-cell subsets are carefully evaluated to determine if further testing is needed for confirmation, including functional assays and genotyping, which is then suggested as follow-up testing in the interpretive report as detailed below. If abnormalities are found in the B-cell phenotyping panel, the specimen will be reflexed to the CVID confirmation panel for assessment of defects in surface expression of B-cell-activating factor receptor (BAFF-R) and transmembrane activator and calcium modulator and cyclophilin ligand (CAML) interactor (TACI) (2 genes/proteins associated with CVID). To conclusively determine if TACI mutations are present, the TACI mutation analysis test by gene sequencing can be ordered (TACI / Transmembrane Activator and CAML Interactor [TACI] Gene, Full Gene Analysis). CVID Confirmation Flow Panel: BAFF-R is normally expressed on over 95% of B cells, while TACI is expressed on a smaller subset of B cells and a proportion of activated T cells. The lack of TACI or BAFF-R surface expression on the appropriate B-cell population is consistent with a CVID defect. Results will be interpreted in the context of the B-cell phenotyping results and correlation to clinical presentation will be recommended.

**Reference Values:**

The appropriate age-related reference values will be provided on the report.

**Clinical References:**


BALLF B-Lymphoblastic Leukemia/Lymphoma, FISH Clinical Information: In the United States the incidence of acute lymphoblastic leukemia (ALL) is roughly 6,000 new cases per year (as of 2009), or approximately 1 in 50,000. ALL accounts for approximately 70% of all childhood leukemia cases (ages 0 to 19 years), making it the most common type of childhood cancer. Approximately 85% of pediatric cases of ALL are B-cell lineage (B-ALL) and 15% are T-cell lineage (T-ALL). It has a peak incidence at 2 to 5 years of age. The incidence decreases with increasing age, before increasing again at around 50 years of age. ALL is slightly more common in males than females. There is an increased incidence of ALL in individuals with Down syndrome, Fanconi anemia, Bloom syndrome, ataxia telangiectasia, X-linked agammaglobulinemia, and severe combined immunodeficiency. The overall cure rate for ALL in children is about 90% and about 45% to 60% of adults have long-term disease-free survival. CRLF2/IGH rearrangements are more commonly observed in patients with Down syndrome or of Hispanic descent. Specific genetic abnormalities are identified in the majority of cases of B-ALL, either by conventional chromosome studies or FISH studies. Each of the genetic subgroups are important to detect and can be critical prognostic markers. The decision for early transplantation may be made if t(9;22)(q34;q11.2), MLL (KMT2A) translocations, RUNX1 duplication/amplification or a hypodiploid clone is identified. In contrast, if ETV6/RUNX1 fusion is detected by FISH or hyperdiploidy is identified by chromosome studies, the patient has a favorable prognosis and transplantation is rarely considered. A newly recognized World Health Organization (WHO) entity BCR-ABL1-like ALL or also known as Philadelphia chromosome-like acute lymphoblastic
leukemia (Ph-like ALL) is increasing in importance due to the poor prognosis seen in pediatric, adolescent, and young adult ALL. Common features of this entity involve rearrangements with tyrosine kinase genes involving the following genes: ABL2, PDGFRB, JAK2, ABL1, CRLF2, and P2RY8. Patients that have failed on conventional therapies have demonstrated favorable responses to targeted therapies when rearrangements involving these specific gene regions have been identified. Evaluation of the MYC gene region is included in all diagnostic B-ALL panels to evaluate for Burkitt lymphoma. If a positive result is obtained, additional testing for the BCL2 and BCL6 gene regions may be considered. A combination of cytogenetic and FISH testing is currently recommended in all pediatric and adult patients to characterize the B-ALL clone for the important prognostic genetic subgroups. A summary of the characteristic chromosome abnormalities identified in B-ALL is listed in the following table. Common Chromosome Abnormalities in B-Acute Lymphoblastic Leukemia Leukemia Type Cytogenetic change Typical demographic Risk category B-Acute Lymphoblastic Leukemia t(12;21)(p13;q22), ETV6(TEL)/RUNX1(AML1) Pediatric Favorable Hyperdiploidy Pediatric Favorable t(1;19)(q23;p13.3), PBX1/TCF3 Pediatric Intermediate t(9;22)(q34;q11.2) BCR/ABL1 Pediatric/Adult Unfavorable iAMP21, RUNX1 Pediatric Unfavorable del(9p), CDKN2A(p16) All ages Variable t(11q23;var), MLL All ages Unfavorable t(4;11)(q21;q23), AFF1(AF4)/MLL All ages Unfavorable t(6;11)(q27;q23), MLLT4/MLL All ages Unfavorable t(9;11)(p22;q23), MLLT3(AF9)/MLL All ages Unfavorable t(10;11)(p12;q23), MLLT10/MLL All ages Unfavorable t(11;19)(q23;p13.1), MLL/ELL All ages Unfavorable t(14q32;var), IGH All ages Variable t(X;14)(p22;q32)/t(Y;14)(p11;q32), CRLF2/IGH Adolescent/Young Adult Unfavorable t(Xp22.33;var) or t(Yp11.32;var), P2RY8 All ages Unfavorable del(17p), TP53 All ages Unfavorable t(q824.1;var), MYC Pediatric/ Adolescent/ Young Adult Complex karyotype (> or =4 abnormalities) Adult Unfavorable Low hypodiploidy/near triploidy Adult Unfavorable Near-haploid/hypodiploid All ages Unfavorable Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL) t(1q25;var), ABL2 Pediatric/ Adolescent/ Young Adult High Risk t(5q33;var), PDGFRB t(9p24.1;var), JAK2 t(9q34;var), ABL1 t(Xp22.33;var) or t(Yp11.32;var), CRLF2 t(Xp22.33;var) or t(Yp11.32;var), P2RY8

**Useful For:** Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with B-cell acute lymphoblastic leukemia (B-ALL) and Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL) Identifying and tracking known chromosome abnormalities in patients with B-ALL and Ph-like ALL and tracking response to therapy As an adjunct to conventional chromosome studies in patients with B-ALL and Ph-like ALL

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**B-Type Natriuretic Peptide (BNP), Plasma**

**Clinical Information:** B-type natriuretic peptide (brain natriuretic peptide; BNP) is a 32-amino acid-ringed peptide secreted by the heart to regulate blood pressure and fluid balance. BNP is stored in and secreted predominantly from membrane granules in the heart ventricles, and is continuously secreted in response to increases in intraventricular pressure. BNP concentrations are increased in the serum of patients with left ventricular dysfunction. BNP is measured to evaluate cardiac function and to aid in the diagnosis of heart failure.

**Clinical Applications:** BNP is used to aid in the diagnosis and evaluation of heart failure, particularly in distinguishing patients with heart failure from those with normal cardiac function. BNP is recommended for monitoring cardiac function in patients with heart failure and identifying patients who may benefit from therapy. BNP is also used to assess the response to therapy in patients with heart failure and to monitor patients for disease progression.

**Clinical Decision Making:** BNP is a useful biomarker for the diagnosis and management of heart failure. It is often used in conjunction with other clinical parameters to determine the presence and severity of heart failure. BNP can help identify patients who are at high risk for heart failure, guide the selection of appropriate treatment, and assess the effectiveness of therapy.

**Interpretation:** The clinical decision-making process for BNP includes the consideration of normal reference ranges, patient demographics, and clinical context. BNP levels can be influenced by various factors, such as age, sex, and concomitant medical conditions. Therefore, the interpretation of BNP results should be made in conjunction with other diagnostic tests and clinical findings.

**Reference Values:**
Normal reference ranges for BNP vary depending on the laboratory and the population. Generally, normal BNP levels are below 100 pg/mL in adults and below 30 pg/mL in children. However, these values can be affected by age, gender, and underlying conditions. Therefore, it is essential to consult the laboratory's reference ranges for a specific population group.

**Clinical References:**
1. BNP: B-Type Natriuretic Peptide. Mayo Clinic. Available at: https://www.mayoclinic.org/diseases-conditions/b-type-natriuretic-peptide/basics/definition-20002563
released from the heart in response to both ventricle volume expansion and pressure overload. The natriuretic peptide system and the renin-angiotensin system counteract each other in arterial pressure regulation. When arterial pressure decreases, the kidneys release renin, which activates angiotensinogen resulting in increased peripheral resistance of the arterioles, thus increasing arterial pressure. The natriuretic peptides counteract the effects of renin secretion, causing a reduction of blood pressure and in extracellular fluid volume. Both BNP and atrial natriuretic peptide (ANP) are activated by atrial and ventricular distension due to increased intracardiac pressure. These peptides have both natriuretic and diuretic properties: they raise sodium and water excretion by increasing the glomerular filtration rate and inhibiting sodium reabsorption by the kidney. The New York Heart Association (NYHA) developed a functional classification system for congestive heart failure (CHF) consisting of 4 stages based on the severity of the symptoms. Various studies have demonstrated that circulating BNP concentrations increase with the severity of CHF based on the NYHA classification.

**Useful For:** Aids in the diagnosis of congestive heart failure (CHF) The role of brain natriuretic peptide in monitoring CHF therapy is under investigation

**Interpretation:**

- normal <200 pg/mL: likely compensated congestive heart failure (CHF)
- or =200 to < or =400 pg/mL: likely moderate CHF
- >400 pg/mL: likely moderate-to-severe CHF

Brain natriuretic peptide (BNP) levels are loosely correlated with New York Heart Association (NYHA) functional class (see Table). Interpretive Levels for CHF Functional Class 5th to 95th Percentile Median I 15 to 499 pg/mL II 10 to 1,080 pg/mL II 22 pg/mL III 38 to >1,300 pg/mL IV 147 to >1,300 pg/mL 1,006 pg/mL All CHF 22 to >1,300 pg/mL 360 pg/mL Elevation in BNP can occur due to right heart failure with cor pulmonale (200-500 pg/mL), pulmonary hypertension (300-500 pg/mL), and acute pulmonary embolism (150-500 pg/mL). Elevations also occur in patients with acute coronary syndromes.

**Reference Values:**

**Males**

- < or =45 years: < or =35 pg/mL
- 46 years: < or =36 pg/mL
- 47 years: < or =37 pg/mL
- 48 years: < or =38 pg/mL
- 49 years: < or =39 pg/mL
- 50 years: < or =40 pg/mL
- 51 years: < or =41 pg/mL
- 52 years: < or =42 pg/mL
- 53 years: < or =43 pg/mL
- 54 years: < or =45 pg/mL
- 55 years: < or =46 pg/mL
- 56 years: < or =47 pg/mL
- 57 years: < or =48 pg/mL
- 58 years: < or =49 pg/mL
- 59 years: < or =51 pg/mL
- 60 years: < or =52 pg/mL
- 61 years: < or =53 pg/mL
- 62 years: < or =55 pg/mL
- 63 years: < or =56 pg/mL
- 64 years: < or =57 pg/mL
- 65 years: < or =59 pg/mL
- 66 years: < or =60 pg/mL
- 67 years: < or =62 pg/mL
- 68 years: < or =64 pg/mL
- 69 years: < or =65 pg/mL
- 70 years: < or =67 pg/mL
- 71 years: < or =69 pg/mL
- 72 years: < or =70 pg/mL
- 73 years: < or =72 pg/mL
- 74 years: < or =74 pg/mL
- 75 years: < or =76 pg/mL
- 76 years: < or =78 pg/mL

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77 years: < or =80 pg/mL
78 years: < or =82 pg/mL
79 years: < or =84 pg/mL
80 years: < or =86 pg/mL
81 years: < or =88 pg/mL
82 years: < or =91 pg/mL
> or =83 years: < or =93 pg/mL
Females
< or =45 years: < or =64 pg/mL
46 years: < or =66 pg/mL
47 years: < or =67 pg/mL
48 years: < or =69 pg/mL
49 years: < or =71 pg/mL
50 years: < or =73 pg/mL
51 years: < or =74 pg/mL
52 years: < or =76 pg/mL
53 years: < or =78 pg/mL
54 years: < or =80 pg/mL
55 years: < or =82 pg/mL
56 years: < or =84 pg/mL
57 years: < or =87 pg/mL
58 years: < or =89 pg/mL
59 years: < or =91 pg/mL
60 years: < or =93 pg/mL
61 years: < or =96 pg/mL
62 years: < or =98 pg/mL
63 years: < or =101 pg/mL
64 years: < or =103 pg/mL
65 years: < or =106 pg/mL
66 years: < or =109 pg/mL
67 years: < or =112 pg/mL
68 years: < or =114 pg/mL
69 years: < or =117 pg/mL
70 years: < or =120 pg/mL
71 years: < or =123 pg/mL
72 years: < or =127 pg/mL
73 years: < or =130 pg/mL
74 years: < or =133 pg/mL
75 years: < or =137 pg/mL
76 years: < or =140 pg/mL
77 years: < or =144 pg/mL
78 years: < or =147 pg/mL
79 years: < or =151 pg/mL
80 years: < or =155 pg/mL
81 years: < or =159 pg/mL
82 years: < or =163 pg/mL
> or =83 years: < or =167 pg/mL

**Babesia microti IgG Antibodies, Serum**

**Clinical Information:** Babesiosis is a zoonotic infection caused by the protozoan parasite *Babesia microti*. The infection is acquired by contact with *Ixodes* ticks carrying the parasite. The deer mouse is the animal reservoir and, overall, the epidemiology of this infection is much like that of Lyme disease. Babesiosis is most prevalent in the Northeast, Upper Midwest, and Pacific Coast of the United States. Infectious forms (sporozoites) are injected during tick bites and the organism enters the vascular system where it infects RBCs. In this intraerythrocytic stage it becomes disseminated throughout the reticuloendothelial system. Asexual reproduction occurs in RBCs, and daughter cells (merozoites) are formed which are liberated on rupture (hemolysis) of the RBC. Most cases of babesiosis are probably subclinical or mild, but the infection can be severe and life threatening, especially in older or asplenic patients. Fever, fatigue, malaise, headache, and other flu-like symptoms occur most commonly. In the most severe cases, hemolysis, acute respiratory distress syndrome, and shock may develop. Patients may have hepatomegaly and splenomegaly. A serologic test can be used as an adjunct in the diagnosis and follow-up of babesiosis, when infection is chronic or persistent, or in seroepidemiologic surveys of the prevalence of the infection in certain populations. Babesiosis is usually diagnosed by observing the organisms in infected RBCs on Giemsa-stained thin blood films of smeared peripheral blood. Serology may also be useful if the parasitemia is too low to detect or if the infection has cleared naturally or following treatment.

**Useful For:** An adjunct in the diagnosis of babesiosis, Follow-up of documented babesiosis

**Interpretation:** A positive result of an indirect fluorescent antibody test (titer ≥ 1:64) suggests current or previous infection with *Babesia microti*. In general, the higher the titer, the more likely it is that the patient has an active infection. Patients with documented infections have usually had titers ranging from 1:320 to 1:2,560.

**Reference Values:**

<1:64

Reference values apply to all ages.


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**Babesia species, Molecular Detection, PCR, Blood**

**Clinical Information:** Babesiosis is a tick-transmitted zoonosis caused by intraerythrocytic protozoa in the genus *Babesia*. *Babesia microti* is responsible for the vast majority of human cases in the United States, with most cases occurring along the Northeast Coast and the upper Midwestern states. A small number of cases of *B duncani* human infection have also been reported along Pacific Coast states from Washington to northern California, and *B divergens/B divergens-like* strains have been detected in humans in Missouri (MO-1 strain), Kentucky, and Washington. In Europe, *B divergens* and *B venatorum* are the primary causes of human babesiosis. Humans most commonly acquire infection through the bite of an infected tick. The most common tick vectors in the United States are *Ixodes scapularis* and *Ixodes pacificus*, while *Ixodes ricinus* and other ticks transmit the parasite in Europe and Asia. Less commonly, babesiosis may be acquired through blood transfusion and across the placenta from the mother to the fetus. Most patients with babesiosis are asymptomatic or have only a self-limited mild flu-like illness, but some develop a severe illness that may result in death. Patient symptoms may include fever, chills, extreme fatigue, and severe anemia. The most severe cases occur in asplenic individuals and those over 50 years of age. Rare cases of chronic parasitemia, usually in immunocompromised patients, have been described. Babesiosis is conventionally diagnosed through microscopic examination of Giemsa-stained thick and thin peripheral blood films looking for characteristic intraerythrocytic *Babesia* parasites. This method is relatively rapid, widely available, and capable of detecting (but not differentiating) human-infective *Babesia* species. It is also necessary for calculating the percentage of parasitemia which is used to predict prognosis, guide patient management, and monitor response to treatment. However, microscopic examination requires skilled microscopists and may be challenging in the setting of low parasitemia or prior drug therapy. Also, *Babesia* species may closely resemble those of *Plasmodium*.
falciparum. The Mayo Clinic real-time PCR assay provides a rapid and more sensitive alternative to blood film examination for detection and differentiation of B microti, B duncani, and B divergens/B divergens-like parasites. It does not cross-react with malaria parasites.

**Useful For:** An initial screening or confirmatory testing method for suspected babesiosis during the acute febrile stage of infection in patients from endemic areas, especially when Giemsa-stained peripheral blood smears do not reveal any organisms or the organism morphology is inconclusive.

**Interpretation:** A positive result indicates the presence of Babesia species DNA and is consistent with active or recent infection. While positive results are highly specific indicators of disease, they should be correlated with blood smear microscopy, serological results and clinical findings. A negative result indicates absence of detectable DNA from Babesia species in the specimen, but does not always rule out ongoing babesiosis in a seropositive person, since the parasitemia may be present at a very low level or may be sporadic. Other tests to consider in the evaluation of a patient presenting with an acute febrile illness following tick exposure include serologic tests for Lyme disease (Borrelia burgdorferi), and molecular detection (PCR) for ehrlichiosis/anaplasmosis. For patients who are past the acute stage of infection, serologic tests for these organisms should be ordered prior to PCR testing.

**Reference Values:**
Negative

**Clinical References:**

**Bacterial Culture, Aerobic**

**Clinical Information:** Sterile Body Fluids and Normally Sterile Tissues: In response to infection, fluid may accumulate in any body cavity. Wound, Abscess, Exudates: Skin and soft tissue infections can occur as a result of a break in the skin surface, or they can occur as complications of surgery; trauma; human, animal, or insect bites; or diseases that interrupt a mucosal or skin surface. Specimen collection is of utmost importance for these specimen types. For most open lesions and abscesses, remove the superficial flora by decontaminating the skin before collecting a specimen from the advancing margin or base. A closed abscess is the specimen site of choice. Aspirate the abscess contents with a syringe.

**Useful For:** Detecting bacteria responsible for infections of sterile body fluids, tissues, or wounds

**Interpretation:** Any microorganism found where no resident flora is present is considered significant and is reported. For specimens contaminated with the usual bacterial flora, bacteria that are potentially pathogenic are identified.

**Reference Values:**
No growth or usual flora
Identification of probable pathogens

**Clinical References:**
**Bacterial Culture, Aerobic, Respiratory**

**Clinical Information:** Common bacterial agents of acute pneumonia include: Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Pseudomonas aeruginosa, and members of the Enterobacteriaceae (Escherichia coli, Klebsiella species, and Enterobacter species) Clinical history, physical examination, and chest X-ray are usually adequate for the diagnosis of pneumonia, and antimicrobial treatment is typically based on these findings. Culture of expectorated sputum is used by some for the evaluation of pneumonia, although controversy exists regarding this practice; both sensitivity and specificity of sputum cultures are generally regarded as poor (<50%). Specificity is improved by collecting expectorated purulent matter from the lower respiratory tract and avoiding mouth and oropharyngeal matter, thereby reducing contamination. Prior to culture, the specimen should be examined for the presence of WBCs (evidence of purulent matter) and a paucity of squamous cells (evidence of minimal contamination by oral matter). Blood cultures should be performed to establish the definitive etiology of an associated pneumonia. However, only 20% to 30% of patients with bacterial pneumonia are bacteremic.

**Useful For:** An aid in the diagnosis of lower respiratory bacterial infections including pneumonia

**Interpretation:** Organisms associated with lower respiratory tract infections are reported.

**Reference Values:**
- No growth or usual flora
- Identification of probable pathogens

**Clinical References:**

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**Bacterial Culture, Aerobic, Urine**

**Clinical Information:** Urinary tract infection (UTI) encompasses a broad range of clinical entities that vary in their clinical presentation, degree of tissue invasion, epidemiologic setting, and antibiotic therapy requirements. There are 4 major types of UTIs: urethritis, cystitis, acute urethral syndrome, and pyelonephritis. UTIs may also be classified as uncomplicated or complicated. Escherichia coli is the leading cause of uncomplicated community-acquired UTI. Risk factors that predispose one to complicated UTIs include: underlying diseases that are associated with kidney infection (eg, diabetes), kidney stones, structural or functional urinary tract abnormalities, and indwelling urinary catheters. Another classification of UTIs is as upper UTI (related to the kidney, renal pelvis, or ureter) or lower UTI (urinary bladder and urethra). The classic symptoms of upper UTI are fever (often with chills) and flank pain; frequent painful urination, urgency, and dysuria are more often associated with lower UTI.

**Useful For:** Diagnosis of urinary tract infections Quantitative culture results may be helpful in discriminating contamination, colonization, and infection.

**Interpretation:** In general, the isolation of more than 100,000 cfu/mL of a urinary pathogen is indicative of urinary tract infection (UTI). Isolation of 2 or more organisms above 10,000 cfu/mL may suggest specimen contamination. For specimens contaminated with the usual bacterial flora, bacteria that are potentially pathogenic are identified.

**Reference Values:**
- No growth or identification of probable pathogens with colony count ranges

**Bacterial Culture, Anaerobic**

**Clinical Information:** Anaerobic bacteria are the greatest component of the human body's normal bacterial flora colonizing the skin, oral cavity, and genitourinary and lower gastrointestinal tracts and generally do not cause infection. Their presence is important for vitamin and other nutrient absorption and in preventing infection with pathogenic bacteria. When usual skin and mucosal barriers are penetrated and in an anaerobic environment, these bacteria can behave as pathogens. Typical anaerobic infections include periodontitis, abdominal or pelvic abscesses, endometritis, pelvic inflammatory disease, aspiration pneumonia, empyema and lung abscesses, sinusitis, brain abscesses, gas gangrene, and other soft tissue infections. Anaerobes grow aggressively in the body under anaerobic conditions and may possess a variety of virulence factors including capsules and extracellular enzymes. They also can develop resistance to antimicrobials by producing beta-lactamase and other modifying enzymes and by alterations in membrane permeability and structure of penicillin-binding proteins. Because anaerobic bacteria are a significant cause of human infection and they are often resistant to commonly used antimicrobials, susceptibility testing results are useful to clinicians. Many Bacteroides species produce beta-lactamases. Imipenem, metronidazole, and clindamycin are effective agents although resistance to clindamycin, and occasionally imipenem, is increasing.

**Useful For:** Diagnosing anaerobic bacterial infections

**Interpretation:** Isolation of anaerobes in significant numbers from well-collected specimens including blood, other normally sterile body fluids, or closed collections of purulent fluid, indicates infection with the identified organisms.

**Reference Values:**
- No growth
- Identification of probable pathogens


**Bacterial Culture, Cystic Fibrosis, Respiratory**

**Clinical Information:** Life expectancy of patients with cystic fibrosis (CF) has increased steadily over the past 50 years, in large part due to improvements in the management of lung disease in this patient population. Still, chronic lung infection is responsible for 75% to 85% of deaths in patients with CF. Appropriate treatment for the causative organism can reduce morbidity and mortality. The number of microbial species associated with CF lung disease is relatively limited. These include Pseudomonas aeruginosa (mucoid and nonmucoid), Staphylococcus aureus, Burkholderia cepacia complex, Stenotrophomonas maltophilia, other nonfermenting gram-negative rods, Haemophilus influenzae, and Streptococcus pneumoniae. Nontuberculous mycobacteria and Aspergillus species may also play a role in CF lung disease, in addition to common respiratory viruses. This culture, which is specifically designed for CF patients, utilizes conventional and additional selective media (compared to non-CF respiratory cultures) to isolate bacteria commonly associated with pulmonary disease in CF patients. In selected centers, lung transplantation is performed on CF patients. This test is appropriate for lung transplant patients with underlying CF because they can continue to harbor the same types of organisms as they did pretransplantation. CF patients may be colonized or chronically infected by these organisms over a long period of time.

**Useful For:** Detection of aerobic bacterial pathogens from cystic fibrosis patient specimens

**Interpretation:** A negative test result is no growth of bacteria or growth of only usual flora. A negative result does not rule out all causes of infectious lung disease (see Cautions). Organisms associated with lower respiratory tract infections are reported. For positive test results, pathogenic bacteria are identified. Cystic fibrosis patients may be colonized or chronically infected by some
organisms over a long period of time, therefore, positive results must be interpreted in conjunction with previous findings and the clinical picture to appropriately evaluate results.

**Reference Values:**
No growth or usual flora
Identification of probable pathogens

**Clinical References:**

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**Bacterial Typing by Pulsed-Field Gel Electrophoresis (PFGE)**

**Clinical Information:** Bacterial-typing techniques are useful for determining strain relatedness in the setting of nosocomial outbreaks or apparent outbreaks. Serial isolates obtained from the same patient can be typed to determine whether they are the same or different. Typing allows discrimination between isolates of the same species, informing recognition of a potential outbreak. In the past, strain typing was accomplished by testing for different biochemical, phage, or antibiotic resistance patterns. Antibiograms are often unreliable because they are easy to over-interpret or under-interpret. Other strain-typing methods are often organism-specific and each requires a unique set of reagents and procedures. The availability of classical strain-typing techniques has been limited.

**Useful For:** Investigating infection outbreaks by a single bacterial species

**Interpretation:** Isolates that show identical DNA restriction fragment length polymorphism patterns are considered to be closely related.

**Reference Values:**
Reported as isolates are "indistinguishable" or "different" by pulsed-field gel electrophoresis.

**Clinical References:**

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**Bacterial Typing by Whole Genome Sequencing**

**Clinical Information:** Bacterial strain typing may be useful for determining strain relatedness in the setting of possible nosocomial transmission or community outbreaks. Serial isolates obtained from the same patient may be typed to assess similarity. Typing may allow discrimination of 2 or more isolates of the same species, which can inform recognition of an outbreak, nosocomial transmission, or identify a potential source of infection in an individual patient. Pulse-field gel electrophoresis (PFGE) has traditionally been used for strain typing, but does not always discriminate between different bacterial strains (eg, 2 genetically dissimilar strains may have indistinguishable PFGE patterns). Whole genome sequencing offers a higher level of resolution of genetic relatedness of strains than does PFGE.

**Useful For:** Aids in investigation of a potential outbreak by a single bacterial species May assist in identification of recurrent infection in an individual patient

**Interpretation:** The genomic sequence of individual isolates will be determined and compared to the genomic sequences of the other cosubmitted isolates. The report will indicate the degree of relatedness between the isolates. A link to the interpretive report will be sent to the registered email address provided...
by the client.

**Reference Values:**
Reported as isolates are "related", "possibly related", or "unrelated" by whole genome sequencing.

**Clinical References:**

**Bahia Grass, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
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**Clinical References:** Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and...
Baker's Yeast, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**FBANG 57635**

**Banana IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

---

**BANA 82746**

**Banana, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
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**BAP1 Immunostain, Technical Component Only**

**Clinical Information:** BRCA1-associated protein 1 (BAP1) is a deubiquitinating enzyme that is a member of the polycomb group proteins of transcriptional repressors and exhibits tumor suppressive activity. BAP1 is located on chromosome 3p21 where loss of 1 copy of the gene and inactivating mutations are associated with the increased risk and development of various tumors such as malignant mesotheliomas, uveal melanomas, clear cell renal cell carcinoma, and esophageal squamous carcinomas. In some of these cases, loss of nuclear staining for BAP1 has been reported.

**Useful For:** As part of a panel of immunostains where loss of staining can be used as a marker of various neoplasms

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
5. Churg A, Sheffield BS, Galateau-Salle F: New markers for Separating Benign from Malignant Mesothelials: Are we there yet?
Barbiturates Confirmation, Chain of Custody, Urine

Clinical Information: Barbiturates represent a class of drugs that were originally introduced as sleep inducers. Butalbital is also used to control severe headaches. Mephobarbital and phenobarbital are frequently used to control major motor (grand mal) seizures. These drugs are commonly abused as "downers" to induce sleep after an amphetamine- or cocaine-induced "high." Chain-of-custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detecting drug abuse involving barbiturates such as amobarbital, butalbital, pentobarbital, phenobarbital, and secobarbital.

Chain-of-custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: The presence of a barbiturate in urine at >200 ng/mL indicates use of 1 of these drugs. Most of the barbiturates are fast acting; their presence indicates use within the past 3 days. Phenobarbital, commonly used to control epilepsy, has a very long half-life. The presence of phenobarbital in urine indicates that the patient has used the drug sometime within the past 30 days.

Reference Values:
Negative
Cutoff concentrations:

IMMUNOASSAY SCREEN
<200 ng/mL

BUTALBITAL BY GC-MS
<100 ng/mL

AMOBARBITAL BY GC-MS
<100 ng/mL

PENTOBARBITAL BY GC-MS
<100 ng/mL

SECOBARBITAL BY GC-MS
<100 ng/mL

PHENOBARBITAL BY GC-MS
<100 ng/mL

**Interpretation:** The presence of a barbiturate in urine at >200 ng/mL indicates use of 1 of these drugs. Most of the barbiturates are fast acting; their presence indicates use within the past 3 days. Phenobarbital, commonly used to control epilepsy, has a very long half-life. The presence of phenobarbital in urine indicates that the patient has used the drug sometime within the past 30 days.

**Reference Values:**

Negative

Cutoff concentrations:

- **BUTALBITAL BY GC-MS**
  - <100 ng/mL

- **AMOBARBITAL BY GC-MS**
  - <100 ng/mL

- **PENTOBARBITAL BY GC-MS**
  - <100 ng/mL

- **SECOBARBITAL BY GC-MS**
  - <100 ng/mL

- **PHENOBARBITAL BY GC-MS**
  - <100 ng/mL

**Clinical References:** Baselt RC, Cravey RH: Disposition of Toxic Drugs and Chemicals in Man. Third edition. Chicago, IL, Year Book Medical Publishers, 1989

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**FBARS**

**Barium, Serum**

**Reference Values:**

Units: ng/mL

Reference range has not been established.

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**BGRS**

**Barley Grass, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
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| 6     | > or =100  | Strongly positive Reference values apply to all ages.


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**FBARG 57578 Barley IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation* 2.0 Upper Limit of Quantitation** 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**BRLY 82687 Barley, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
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**FBART 91439**

**Bartonella Antibody Panel, IFA CSF**

**Reference Values:**

REFERENCE RANGE: <1:1

**INTERPRETIVE CRITERIA:**

<1:1 Antibody Not Detected

> or = 1:1 Antibody Detected

Infection with Bartonella henselae has been associated with cat scratch disease, bacillary angiomatosis, peliosis hepatitis and febrile bacteremia syndrome. Infection with Bartonella quintana has been associated with trench fever and bacillary angiomatosis in both HIV positive and negative individuals.

IgG crossreactivity between B. henselae and B. Quintana may occur at any titer; however, the infecting species will typically have the higher IgG titer. Crossreactivity of IgM between the two species is limited and typically is not seen.

Diagnosis of infections of the central nervous system can be accomplished by demonstrating the presence of intrathecally-produced specific antibody. However, interpreting results is complicated by low antibody levels found in CSF, passive transfer of antibody from blood, and contamination via bloody taps.

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**BART 81575**

**Bartonella Antibody Panel, IgG and IgM, Serum**

**Clinical Information:** Bartonella henselae and Bartonella quintana are small, rod-shaped, pleomorphic, gram-negative bacteria. The human body louse (Pediculus humanis) is the proposed vector for B quintana. No animal reservoir has been determined for B quintana. The domestic cat is believed to be both a reservoir and vector for B henselae. Cats may infect humans directly through scratches, bites, or licks, or indirectly through an arthropod vector. Humans remain the only host in which Bartonella infection leads to significant disease. The sight of entry for Bartonella is through openings in the skin. Microscopically, Bartonella lesions appear as rounded aggregates that proliferate...
rapidly. These aggregates are masses of Bartonella bacteria. Warthin-Starry-staining has shown that Bartonella organisms can be present within the vacuoles of endothelial cells, in macrophages, and between cells in areas of necrosis. Occasionally organisms are seen in the lumens of vessels. While cutaneous lesions are common, disseminated tissue infection by Bartonella has been seen in the blood, lymph nodes, spleen, liver, bone marrow, and heart. B henselae has been associated with cat scratch disease (CSD), peliosis hepatitis (PH), bacillary angiomatosis (BA), and endocarditis. B quintana has been associated with trench fever, BA, and endocarditis. BA is a vascular proliferative disease usually involving the skin and regional lymph nodes. CSD begins as a cutaneous papule or pustule that usually develops within a week after an animal contact. Regional lymphadenopathy, which follows, is the predominant clinical feature of CSD. Trench fever, which was a significant problem during World War I and World War II, is characterized by a relapsing fever and severe pain in the shins. PH and febrile bacteremia syndrome are both syndromes that have afflicted patients with AIDS or those patients who are immunocompromised. While trench fever and CSD are usually self-limiting illnesses, the other Bartonella-associated diseases can be life-threatening. Interest in B quintana and B henselae has recently increased since its increased prevalence in patients with AIDS, in transplant patients, and those with suppressed immunity.

**Useful For:** Diagnosis of Bartonella infection, especially in the context of a cat scratch

**Interpretation:** A positive immunofluorescence assay (IFA) IgM (titer >1:20) suggests a current infection with either Bartonella henselae or B quintana. A positive IgG (titer >1:128) suggests a current or previous infection. Increases in IgG titers in serial specimens suggest active infection. Normal serum specimens usually have an IgG titer of less than 1:128. However, 5% to 10% of healthy controls exhibit a B henselae and B quintana titer of 1:128. Sera from healthy volunteers rarely show titers of 1:256 or greater. IgM titers in normal serum are typically less than 1:20. IgM titers at 1:20 or greater have not been seen in the normal population. Molecular testing of tissue for Bartonella species nucleic acid is recommended in cases of suspected endocarditis.

**Reference Values:**

Bartonella henselae
- IgG: <1:128
- IgM: <1:20

Bartonella quintana
- IgG: <1:128
- IgM: <1:20

**Clinical References:**

**BARRP 84440**

**Bartonella, Molecular Detection, PCR**

**Clinical Information:** Bartonella henselae and B quintana are small, pleomorphic Gram stain-negative bacilli that are difficult to isolate by culture due to their fastidious growth requirements. B henselae has been associated with cat scratch disease, bacillary angiomatosis, peliosis hepatitis, and endocarditis. B quintana has been associated with trench fever, bacillary angiomatosis, and endocarditis. The diagnosis of Bartonella infection has traditionally been made by Warthin-Starry staining of infected tissue or serology. However, these methods may be falsely negative or nonspecific, respectively. Culture is insensitive. Evaluation of infected tissue using PCR has been shown to be an effective tool for diagnosing Bartonella infection. Mayo Medical Laboratories has developed a real-time PCR test that permits rapid identification of Bartonella species. The assay targets a unique sequence of the citrate synthase gene present in Bartonella species.

**Useful For:** Diagnosing Bartonella infection
Interpretation: A positive test indicates the presence of Bartonella species DNA. A negative test indicates the absence of detectable DNA, but does not negate the presence of the organism or recent disease as false-negative results may occur due to inhibition of PCR, sequence variability underlying primers or probes, or the presence of Bartonella DNA in quantities less than the limit of detection of the assay.

Reference Values: Not applicable


BARTB
89983

Bartonella, Molecular Detection, PCR, Blood

Clinical Information: Bartonella henselae and B. quintana are small, pleomorphic, gram-negative bacilli that are difficult to isolate by culture due to their fastidious growth requirements. B. henselae has been associated with cat scratch disease, bacillary angiomatosis, peliosis hepatitis, and endocarditis. B. quintana has been associated with trench fever, bacillary angiomatosis, and endocarditis. The diagnosis of Bartonella infection has traditionally been made by Warthin-Starry staining of infected tissue and serology. However, these methods may be nonspecific or falsely negative, especially in the early stages of disease. Evaluation of infected tissue or blood using PCR has been shown to be an effective tool for diagnosing Bartonella infection. Mayo Medical Laboratories has developed a real-time PCR test that permits rapid identification of Bartonella species. The assay targets a unique sequence of the citrate synthase (gltA) gene present in Bartonella species.

Useful For: Diagnosing Bartonella infection when Bartonella DNA would be expected to be present in blood, especially endocarditis

Interpretation: A positive test indicates the presence of Bartonella species DNA. A negative test indicates the absence of detectable DNA, but does not negate the presence of the organism or recent disease as false-negative results may occur due to inhibition of PCR, sequence variability underlying primers or probes, or the presence of Bartonella DNA in quantities less than the limit of detection of the assay.

Reference Values: Not applicable


BMAMA
113630

Basic Metabolic Panel, Serum

Clinical Information: The basic metabolic panel measures 8 analytes and calculates an anion gap. It is used to assess kidney status, electrolyte, and acid/base balance, and blood glucose.

Useful For: Routine health monitoring or patient monitoring while hospitalized for information regarding metabolism, including the current kidney status, electrolyte, and acid/base balance, and blood glucose
**Interpretation:** Basic metabolic panel results are usually evaluated in conjunction with each other for patterns of results. A single abnormal test result could be indicative of something different than if more than 1 of the test results are abnormal. Many conditions will cause abnormal results including kidney failure, breathing problems, and diabetes-related complications.

**Reference Values:**

- **SODIUM**
  - <1 year: not established
  - ≥1 year: 135-145 mmol/L

- **POTASSIUM**
  - <1 year: not established
  - ≥1 year: 3.6-5.2 mmol/L

- **CHLORIDE**
  - <1 year: not established
  - 1-17 years: 102-112 mmol/L
  - ≥18 years: 98-107 mmol/L

- **BICARBONATE**
  - Males:
    - <1 year: not established
    - 1-2 years: 17-25 mmol/L
    - 3 years: 18-26 mmol/L
    - 4-5 years: 19-27 mmol/L
    - 6-7 years: 20-28 mmol/L
    - 8-17 years: 21-29 mmol/L
  - ≥18 years: 22-29 mmol/L
  - Females:
    - <1 year: not established
    - 1-3 years: 18-25 mmol/L
    - 4-5 years: 19-26 mmol/L
    - 6-7 years: 20-27 mmol/L
    - 8-9 years: 21-28 mmol/L
    - ≥10 years: 22-29 mmol/L

- **ANION GAP**
  - <7 years: not established
  - ≥7 years: 7-15

- **BLOOD UREA NITROGEN**
  - Males:
    - <12 months: not established
    - 1-17 years: 7-20 mg/dL
  - ≥18 years: 8-24 mg/dL
  - Females:
    - <12 months: not established
    - 1-17 years: 7-20 mg/dL
  - ≥18 years: 6-21 mg/dL

- **CREATININE**
  - Males:
    - 0-11 months: 0.17-0.42 mg/dL
    - 1-5 years: 0.19-0.49 mg/dL
    - 6-10 years: 0.26-0.61 mg/dL
11-14 years: 0.35-0.86 mg/dL
> or =15 years: 0.74-1.35 mg/dL

Females:
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-15 years: 0.35-0.86 mg/dL
> or =16 years: 0.59-1.04 mg/dL

ESTIMATED GLOMERULAR FILTRATION RATE (eGFR)
>60 mL/min/BSA
Estimated GFR calculated using the 2009 CKD_EPI creatinine equation

CALCIUM
<1 year: 8.7-11.0 mg/dL
1-17 years: 9.3-10.6 mg/dL
18-59 years: 8.6-10.0 mg/dL
60-90 years: 8.8-10.2 mg/dL
>90 years: 8.2-9.6 mg/dL

GLUCOSE
0-11 months: not established
> or =1 year: 70-140 mg/dL


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**FBSLG**

**57660**

**Basil IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**BASL**

**82489**

**Basil, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or an anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;0.35</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Bass Black (Sea Bass) (Centropristis striata) IgE**

**Interpretation:** Class IgE(kU/L) Comment 0 <0.35 Below Detection 1 0.35 - 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:** <0.35 kU/L

**Bay Leaf, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to...
identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;0.10</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.10 - 0.34</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.35 - 1.7</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>1.71 - 17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5 - 49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0 - 99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**FBWME 57583**

**Bayberry/Wax Myrtle (Myrica spp) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal 1 0.35 - 0.69 Low Positive 2 0.70 - 3.4 Moderate Positive 3 3.5 - 17.4 High Positive 4 5 6 17.5 - 49.9 50.0 - 99.9 > or = 100 Very High Positive Very High Positive Very High Positive Very High Positive

**Reference Values:**

<0.35 kU/L

**BCL2 70362**

**BCL-2 Immunostain, Technical Component Only**

**Clinical Information:** BCL-2 is in a family of regulators of apoptosis, which together control the balance between pro- and antiapoptotic signals. BCL-2 protein acts as an inhibitor of apoptosis. It is normally expressed in mantle zone B cells and T cells, with an intense perinuclear cytoplasmic pattern, but it is not expressed in reactive germinal center B cells. In the majority of cases of follicular lymphoma, the BCL-2 gene is involved in a translocation with IgH, t(14;18)(q32;q21), leading to overexpression of the BCL-2 protein. Thus, BCL-2 expression in germinal center B cells supports a diagnosis of follicular lymphoma.

**Useful For:** Classification of lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant
quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**BCL6 70363**

**BCL-6 Immunostain, Technical Component Only**

**Clinical Information:** BCL-6 protein is a transcription factor expressed by follicle center B cells and other cells of the follicle center and is useful in the classification of lymphomas.

**Useful For:** Classification of lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**BA190 83336**

**BCR/ABL, p190, mRNA Detection, Reverse Transcription-PCR (RT-PCR), Quantitative, Monitoring Assay**

**Clinical Information:** mRNA transcribed from BCR/ABL (fusion of the breakpoint cluster region gene [BCR]at chromosome 22q11 to the Abelson gene [ABL] at chromosome 9q23) is detected in all chronic myelogenous leukemia (CML) patients and a subset of both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) patients. Although breakpoints in the BCR and ABL genes may occur in a variety of locations, splicing of the primary RNA transcripts result in only 8 fusion site variants (e1/a2, e6/a2, e13/a2, e14/a2, e19/a2, and e1/a3, e13/a3, e14/a3), which incorporate the entire sequence of the exons on both sides of the fusion site. The e1/a2 and e1/a3 fusion forms produce a 190-kDa protein designated p190. This bcr/abl protein form is found in approximately 75% of childhood ALL patients and approximately 50% of adult ALL patients, with the majority arising from e1/a2 mRNA. The p190 is also the predominant fusion form in a small subset of CML patients, although the vast majority of CML cases contain the p210 protein, typically from e13/a2 or e14/a2 mRNA fusions. Other fusion forms are very rare. Quantitative reverse-transcription PCR (qRT-PCR) is the most sensitive method for monitoring bcr/abl levels during treatment. This test detects mRNA coding for the most common p190 fusion form (e1/a2).

**Useful For:** Monitoring response to therapy in patients with known e1/a2 bcr/abl (p190) fusion forms
Interpretation: An interpretive report will be provided.

Reference Values:
The presence or absence of the BCR/ABL mRNA (bcr/abl) fusion form producing the p190 fusion protein is reported. If positive, the level is reported as the ratio of bcr/abl (p190) to abl with conversion to a percentage (ie, bcr/abl (p190) as a percentage of total abl).

Clinical References:

BCRFX 65248

BCR/ABL1 Qualitative Diagnostic Assay with Reflex to BCR/ABL1 p190 Quantitative Assay or BCR/ABL1 p210 Quantitative Assay

Clinical Information: The t(9;22)/BCR-ABL1 abnormality is associated with chronic myelogenous leukemia (CML) and "Philadelphia positive" acute lymphoblastic leukemia of B-cell lineage (Ph ALL). Very rarely, this abnormality has also been identified in cases of acute myeloid leukemia and T-lymphoblastic leukemia/lymphoma. The fusion gene on the derivative chromosome 22q11 produces a chimeric BCR-ABL1 mRNA transcript and corresponding translated oncoprotein. Despite substantial breakpoint heterogeneity at the DNA level, a consistent set of BCR-ABL1 mRNA transcripts are produced that can be readily and sensitively detected by reverse transcription PCR (RT-PCR) technique. In CML, breakpoints in BCR result in either exons 13 or 14 (e13, e14) joined to exon 2 of ABL1 (a2). The corresponding e13-a2 or e14-a2 BCR-ABL1 mRNAs produce a 210 kD protein (p210). Rare cases of CML are characterized by an e19-a2 type mRNA with a corresponding p230 protein. In Ph ALL, the majority of cases harbor an e1-a2 BCR-ABL1 mRNA transcript, producing a p190 protein. However, chimeric mRNA type is not invariably associated with disease type, as noted by the presence of p210-positive Ph ALL and very rare cases of p190-positive CML. Therefore, positive results from a screening (diagnostic) assay for BCR-ABL1 mRNA need to be correlated with clinical and pathologic findings. In addition to the main transcript variants described above, rare occurrences of both CML and Ph ALL can have alternative break-fusion events resulting in unusual BCR-ABL1 transcript types. Examples include e6-a2 and BCR exon fusions to ABL1 exon a3 (eg, e13-a3, e14-a3, or e1-a3). In addition to detecting common BCR-ABL1 mRNA transcripts, this assay also can identify these rarer BCR-ABL1 transcript variants and is therefore a comprehensive screen for both usual and uncommon BCR-ABL1 gene fusions in hematopoietic malignancies. Given the nature of genetic events in tumors however, this assay will not identify extremely rare and unexpected BCR-ABL1 events involving other exons (eg, case report level) and is therefore not absolutely specific, but is predicted to detect greater than 99.5% of BCR-ABL1 events. Therefore, it is recommended that for diagnosis, RT-PCR plus a second method (eg, BCR-ABL1 FISH or cytogenetics) should be used. However, this RT-PCR assay is invaluable at diagnosis for identifying the precise BCR-ABL1 mRNA type (eg, for future quantitative assay disease monitoring), which complementary methods cannot. This assay is intended as a qualitative method, providing information on the presence (and specific mRNA type) or absence of the BCR-ABL1 mRNA. Results from this test can be used to determine the correct subsequent assay for monitoring of transcript levels following therapy (eg, BCRAB, BA190). Because the assay is analytically sensitive, it compensates for situations such as partially degraded RNA quality, or low cell number but it is not intended for quantitative or monitoring purposes.

Useful For:
Diagnostic workup of patients with high probability of BCR-ABL1-positive hematopoietic neoplasms, predominantly chronic myeloid/myelogenous leukemia and acute lymphoblastic leukemia. When positive, the test identifies which specific mRNA fusion variant is present to guide selection of an appropriate monitoring assay.
Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.


BCR/ABL1 Translocation (9;22), FISH

Clinical Information: Fusion of BCR/ABL1 is observed in all patients with chronic myeloid leukemia (CML), in approximately 25% of adult patients with precursor B-cell acute lymphoblastic leukemia (B-ALL) and in 1% of patients with pediatric B-ALL. The chromosome mechanism resulting in BCR/ABL1 fusion is a t(9;22)(q34;q11.2) in approximately 85%, a complex 9:22 translocation with 1 or more additional chromosomes in approximately 15% and a chromosomally "cryptic" or insertional translocation in fewer than 1% of patients. Conventional cytogenetic studies are still the gold standard for identification of the t(9;22) and to monitor the effectiveness of treatment in post-therapy bone marrow specimens. FISH testing for BCR/ABL1 fusion or RT-PCR testing for p190 or p210 fusion forms are the recommended tests for evaluation of minimal residual disease following the disappearance of the t(9;22) in a post-treatment chromosome analysis. BCR/ABL1/ASS can be performed on bone marrow or peripheral blood and can be used to establish the percentage of neoplastic interphase nuclei for patients with CML at diagnosis and at all times during treatment, even in cytogenetic remission. BCR/ABL1/ASS can detect all known forms of the Ph chromosome, all atypical patterns associated with t(9;22)(q34q11.2) and can detect low levels of residual disease. We recommend BCR/ABL1/ASS at diagnosis subsequently to monitor the response to therapy.

Useful For: Detecting a neoplastic clone associated with a BCR/ABL1 rearrangement in patients with chronic myeloid leukemia (CML) Tracking the percentage of nuclei with BCR/ABL1 rearrangement and response to therapy in patients with CML

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range. Additional cells are analyzed to assess minimal residual disease (MRD). The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

Reference Values:
An interpretive report will be provided.

chimeric BCR-ABL1 mRNA transcript and corresponding translated oncoprotein. Despite substantial breakpoint heterogeneity at the DNA level, a consistent set of BCR-ABL1 mRNA transcripts are produced that can be readily and sensitively detected by reverse transcription PCR (RT-PCR) technique. In CML, breakpoints in BCR nearly always result in either exons 13 or 14 (e13, e14) joined to exon 2 of ABL1 (a2). The corresponding e13-a2 or e14-a2 BCR-ABL1 mRNAs produce a 210 kDa protein (p210). Rare cases of CML are characterized by an e19-a2 type mRNA with a corresponding p230 protein. In Ph ALL, the majority of cases harbor an e1-a2 BCR-ABL1 mRNA transcript, producing a p190 protein, although some ALL patients may alternatively present with the e13/e14-a2 or p210 type fusion. This assay provides information at the time of diagnosis regarding the presence (and specific mRNA type) or absence of the BCR-ABL1 mRNA. If positive, the reflex test will follow to provide an initial quantitative level of the specific BCR-ABL1 transcript. For example, when positive for the e1-a2 (p190) type mRNA, the reflex test provides a corresponding p190 quantitative value. Results from this test are also useful to determine the correct quantitative assay for subsequent monitoring of transcript levels (ie, p190 or p210) during tyrosine kinase inhibitor therapy.

**Useful For:** Diagnostic workup of patients with a high probability of BCR-ABL1-positive hematopoietic neoplasms, particularly acute lymphoblastic leukemia (B-lymphoblastic leukemia), to provide a pretreatment quantitative level of BCR-ABL1 mRNA transcript if the initial diagnostic RT-PCR screen is positive. When positive, the reflex test provides a quantitative value for the corresponding e1-a2 (p190) BCR-ABL1 mRNA fusion variant.

**Interpretation:** An interpretive report will be provided under the BCRFX / BCR/ABL1 Qualitative Diagnostic Assay with Reflex to BCR/ABL1 p190 Quantitative Assay or BCR/ABL1 p210.

**Reference Values:**
Only orderable as a reflex. See BCRFX / BCR/ABL1 Qualitative Diagnostic Assay with Reflex to BCR/ABL1 p190 Quantitative Assay or BCR/ABL1 p210.

**BCRAB**

**BCR/ABL1, p210, mRNA Detection, Reverse Transcription-PCR (RT-PCR), Quantitative, Monitoring Chronic Myeloid Leukemia (CML)**

**Clinical Information:** Chronic myeloid leukemia (CML) is a hematopoietic stem cell neoplasm included in the broader diagnostic category of myeloproliferative neoplasms. CML is consistently associated with fusion of the breakpoint cluster region gene (BCR) at chromosome 22q11 to the Abelson gene (ABL1) at chromosome 9q23. This fusion is designated BCR/ABL1 and may be seen on routine karyotype as the Philadelphia chromosome. Although various breakpoints within the BCR and ABL1 genes have been described, more than 95% of CMLs contain a consistent mRNA transcript in which either the BCR exon 13 (e13) or BCR exon 14 (e14) is fused to the ABL1 exon 2 (a2), yielding fusion forms e13/a2 and e14/a2, respectively. The e13/a2 and e14/a2 fusion forms produce a 210-kDa protein (p210). The p210 fusion protein is an abnormal tyrosine kinase known to be critical for the clinical and pathologic features of CML, and agents that block the tyrosine kinase activity (ie, tyrosine kinase inhibitors or TKI, such as imatinib mesylate) have been used successfully for treatment. Monitoring the level of BCR/ABL1 mRNA in CML patients during treatment is helpful for both prognosis and management of therapy. Rising BCR/ABL1 mRNA levels following attainment of critical therapeutic milestones (see Clinical References) can be indicative of acquired resistance mutations involving the ABL1 portion of the BCR/ABL1 fusion gene. Quantitative reverse-transcription PCR (qRT-PCR) is the most sensitive method for monitoring BCR-ABL1 levels during treatment. This test detects the BCR/ABL1 mRNA fusion forms found in CML (e13/a2 and e14/a2).

**Useful For:** Monitoring response to therapy in patients with chronic myeloid leukemia who are known to have the e13/a2 or e14/a2 BCR/ABL1 fusion transcript forms.

**Interpretation:** An interpretive report will be provided. When BCR/ABL1 mRNA is present, quantitative results are reported on the international scale (IS), established from data originally reported in the IRIS (International Randomized Study of Interferon versus STI571) trial involving newly diagnosed chronic myeloid leukemia patients. Using the IS, a result of less than 0.1% BCR/ABL1...
ABL1 is equivalent to a major molecular remission. This value is also designated on a log scale (Molecular Response, MR) as MR3. For further discussion of the international scale, see Clinical References.

Reference Values:
The presence or absence of BCR/ABL1 mRNA fusion form e13/e14-a2 producing the p210 fusion protein is identified. If positive, the quantitative level is reported as the normalized ratio of BCR/ABL1 (p210) to endogenous ABL1 mRNA with conversion to a percentage referenced to the international scale (IS), on which 0.1% BCR/ABL1:ABL1 (also represented on a log scale as Molecular Response 3, or MR3) is designated as a major molecular response (MMR) threshold.


B210R 48390

BCR/ABL1, p210, mRNA Detection, Reverse Transcription-PCR (RT-PCR), Quantitative, Reflex

Clinical Information: The t(9;22)/BCR-ABL1 abnormality is associated with chronic myeloid leukemia (CML) and "Philadelphia positive" acute lymphoblastic leukemia of B-cell lineage (Ph ALL). Very rarely, this abnormality has also been identified in cases of acute myeloid leukemia and T-lymphoblastic leukemia/lymphoma. The fusion gene on the derivative chromosome 22q11 produces a chimeric BCR-ABL1 mRNA transcript and corresponding translated oncoprotein. Despite substantial breakpoint heterogeneity at the DNA level, a consistent set of BCR-ABL1 mRNA transcripts are produced that can be readily and sensitively detected by reverse transcription PCR (RT-PCR) technique. In CML, breakpoints in BCR nearly always result in either exons 13 or 14 (e13, e14) joined to exon 2 of ABL1 (a2). The corresponding e13-a2 or e14-a2 BCR-ABL1 mRNAs produce a 210 kD protein (p210). Rare cases of CML are characterized by an e19-a2 type mRNA with a corresponding p230 protein. In Ph ALL, the majority of cases harbor an e1-a2 BCR-ABL1 mRNA transcript, producing a p190 protein, although some ALL patients may alternatively present with the e13/e14-a2 or p210 type fusion. This assay provides information at the time of diagnosis regarding the presence (and specific mRNA type) or absence of the BCR-ABL1 mRNA. If positive, the reflex test will follow to provide an initial quantitative level of the specific BCR-ABL1 transcript. For example, when positive for the e13/e14-a2 (p210) type mRNA, the reflex test provides a corresponding p210 quantitative value. Results from this test are also useful to determine the correct quantitative assay for subsequent monitoring of transcript levels (ie, p190 or p210) during tyrosine kinase inhibitor therapy.

Useful For: Diagnostic workup of patients with a high probability of BCR-ABL1-positive hematopoietic neoplasms, particularly chronic myeloid leukemia and Ph+ acute lymphoblastic leukemia (B-lymphoblastic leukemia), to provide a pretreatment quantitative level of BCR-ABL1 mRNA transcript if the initial diagnostic RT-PCR screen is positive. When positive, the reflex test provides a quantitative value for the corresponding e13-a2 or e14-a2 (p210) BCR-ABL1 mRNA fusion variant

Interpretation: An interpretative report will be provided under the BCRFX / BCR/ABL1 Qualitative Diagnostic Assay with Reflex to BCR/ABL1 p190 Quantitative Assay or BCR/ABL1 p210.

Reference Values:
Only orderable as a reflex. See BCRFX / BCR/ABL1 Qualitative Diagnostic Assay with Reflex to BCR/ABL1 p190 Quantitative Assay or BCR/ABL1 p210.
BCR/ABL1, Qualitative, Diagnostic Assay

Clinical Information: The t(9;22)/BCR-ABL1 abnormality is associated with chronic myelogenous leukemia (CML) and “Philadelphia positive” acute lymphoblastic leukemia of B-cell lineage (Ph ALL). Very rarely, this abnormality has also been identified in cases of acute myeloid leukemia and T-lymphoblastic leukemia/lymphoma. The fusion gene on the derivative chromosome 22q11 produces a chimeric BCR-ABL1 mRNA transcript and corresponding translated oncoprotein. Despite substantial breakpoint heterogeneity at the DNA level, a consistent set of BCR-ABL1 mRNA transcripts are produced that can be readily and sensitively detected by reverse transcription PCR (RT-PCR) technique. In CML, breakpoints in BCR result in either exons 13 or 14 (e13, e14) joined to exon 2 of ABL1 (a2). The corresponding e13-a2 or e14-a2 BCR-ABL1 mRNAs produce a 210 kD protein (p210). Rare cases of CML are characterized by an e19-a2 type mRNA with a corresponding p230 protein. In Ph ALL, the majority of cases harbor an e1-a2 BCR-ABL1 mRNA transcript, producing a p190 protein. However, chimeric mRNA type is not invariably associated with disease type, as noted by the presence of p210-positive Ph ALL and very rare cases of p190-positive CML. Therefore, positive results from a screening (diagnostic) assay for BCR-ABL1 mRNA need to be correlated with clinical and pathologic findings. In addition to the main transcript variants described above, rare occurrences of both CML and Ph ALL can have alternative break-fusion events resulting in unusual BCR-ABL1 transcript types. Examples include e6-a2 and BCR exon fusions to ABL1 exon a3 (eg, e13-a3, e14-a3, or e1-a3). In addition to detecting common BCR-ABL1 mRNA transcripts, this assay also can identify these rarer BCR-ABL1 gene fusions in hematopoietic malignancies. Given the nature of genetic events in tumors however, this assay will not identify extremely rare and unexpected BCR-ABL1 events involving other exons (eg, case report level) and is therefore not absolutely specific, but is predicted to detect >99.5% of BCR-ABL1 events. Therefore, it is recommended that for diagnosis, RT-PCR plus a second method (eg, BCR-ABL1 FISH or cytogenetics) should be used. However, this RT-PCR assay is invaluable at diagnosis for identifying the precise BCR-ABL1 mRNA type (eg, for future quantitative assay disease monitoring), which complementary methods cannot. This assay is intended as a qualitative method, providing information on the presence (and specific mRNA type) or absence of the BCR-ABL1 mRNA. Results from this test can be used to determine the correct subsequent assay for monitoring of transcript levels following therapy (eg, BCRAB, BA190). Because the assay is analytically sensitive, it compensates for situations such as partially degraded RNA quality, or low cell number but it is not intended for quantitative or monitoring purposes.

Useful For: Diagnostic workup of patients with high probability of BCR-ABL1-positive hematopoietic neoplasms, predominantly chronic myelogenous leukemia and acute lymphoblastic leukemia. When positive, the test identifies which specific mRNA fusion variant is present to guide selection of an appropriate monitoring assay. If a quantitative monitoring assay is not available for a rare fusion variant, this assay may be of some value for monitoring.

Interpretation: An interpretive report will be provided.

Reference Values: A qualitative result is provided that indicates the presence or absence of BCR/ABL mRNA. When positive, the fusion variant is also reported.


BCR/ABL1, Tyrosine Kinase Inhibitor Resistance, Kinase Domain Mutation Screen, Sanger Sequencing

Clinical Information: Chronic myelogenous leukemia (CML) is characterized by the presence of the t(9;22) BCR-ABL1 abnormality, resulting in formation of a fusion BCR-ABL1 mRNA and protein.
The ABL1 component of this oncoprotein contains tyrosine kinase activity and is thought to play a central role in the proliferative phenotype of this leukemia. Recent advances have resulted in a number of therapeutic drugs that inhibit the ABL1 tyrosine kinase, as well as other protein tyrosine kinases. Imatinib mesylate (Gleevec, Novartis) is the prototype of these tyrosine kinase inhibitors (TKIs), which are capable of inducing durable hematologic and (in most patients) cytogentic remissions. Unfortunately, a significant subset of patients can develop functional resistance to TKIs, due in a large number of cases (approximately 50%) to the acquisition of point mutations in the kinase domain (KD) of the chimeric ABL1 gene. To date, over 50 distinct mutations have been described, although a smaller subset of these (<20) account for the majority of patients with clinical resistance to TKIs, or have well documented in vitro data in the published literature. Recognition of TKI resistance is important in CML, as the effect of some mutations can be overcome by increasing imatinib dosage, whereas others require switching to either a different (second-generation) TKI, or alternative therapy. The common T315I KD mutation is particularly important, given that this alteration confers pan-resistance to all currently employed TKIs except ponatinib. Typically, TKI resistance is suspected in a CML patient who shows loss of initial therapeutic response (eg, cyogenetic relapse), or a significant and sustained increase in molecular BCR-ABL1 quantitative levels. Similar considerations are also present in patients with Philadelphia chromosome positive B-cell acute lymphoblastic leukemia, who can also be treated using TKI therapy. Point mutations in the oncogenic BCR-ABL1 are typically detected by direct sequencing of PCR products, following RT-PCR amplification of the BCR-ABL mRNA transcript from a peripheral blood specimen. This approach ensures comprehensive screening of the clinically relevant KD region. Because this technique requires inclusion of a longer region of ABL1 in the BCR-ABL1 RT-PCR product, low levels of the BCR-ABL1 mRNA transcript (below 0.01% normalized BCR-ABL1 on the International Scale, IS) may not be efficiently amplified (in contrast to similar amplicons generated by quantitative RT-PCR for diagnosis or monitoring).

Useful For: Evaluating patients with chronic myelogenous leukemia and Philadelphia chromosome positive B-cell acute lymphoblastic leukemia receiving tyrosine kinase inhibitor (TKI) therapy, who are apparently failing treatment Preferred initial test to identify the presence of acquired BCR-ABL1 mutations associated with TKI-resistance

Interpretation: The presence of one or more point mutations in the translocated portion of the ABL1 region of the BCR-ABL1 fusion mRNA is considered a positive result, indicating tyrosine kinase inhibitor (TKI) resistance. The specific type of mutation may influence the sensitivity to a specific TKI, and could be useful in guiding therapeutic options for an individual patient.

Reference Values:
An interpretive report will be provided.

Clinical References:

Bean Black (Phaseolus spp) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:
<0.35 kU/L
Bean Coffee Green IgG

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<23 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Bean Green/String IgG

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation* 2.0 Upper Limit of Quantitation** 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Bean Kidney IgG

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Bean Lima (Phaseolus limensis) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal 1 0.35 - 0.69 Low Positive 2 0.70 - 3.4 Moderate Positive 3 3.5 - 17.4 High Positive 4 17.5 - 49.9 50.0 - 99.9 > or = 100 Very High Positive

**Reference Values:**
<0.35 kU/L

Bean Navy/White (Phaseolus vulgaris) IgE

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 273
**Interpretation:**
Class IgE (kU/L)
- Comment 0 <0.10 Negative
- 0.10 – 0.34 Equivocal/Borderline
- 0.35 – 0.69 Low Positive
- 0.70 – 3.49 Moderate Positive
- 3.50 – 17.49 High Positive
- 17.50 – 49.99 Very High Positive
- >99.99 Very High Positive

**Reference Values:**
<0.35 kU/L

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**FBNWG 57655 Bean Navy/White IgG**

**Interpretation:** mcg/mL of IgG
- Lower Limit of Quantitation 2.0
- Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**BWRS 35376 Beckwith-Wiedemann Syndrome (BWS)/Russell-Silver Syndrome (RSS) Molecular Analysis**

**Clinical Information:** Beckwith-Wiedemann syndrome (BWS) is a disorder characterized by prenatal and/or postnatal overgrowth, neonatal hypoglycemia, congenital malformations, and an increased risk for embryonal tumors. Physical findings are variable and can include abdominal wall defects, macroglossia, and hemihyperplasia. The predisposition for tumor development is associated with specific tumor types such as adrenal carcinoma, nephroblastoma (Wilms tumor), hepatoblastoma, and rhabdomyosarcoma. In infancy, BWS has a mortality rate of approximately 20%. Current data suggest that the etiology of BWS is due to dysregulation of imprinted genes in the 11p15 region of chromosome 11, including H19 (maternally expressed), LIT1 (official symbol KCNQ1OT1; paternally expressed), IGF2 (paternally expressed), and CDKN1C (aliases p57 and KIP2; maternally expressed). Expression of these genes is controlled by 2 imprinting centers (IC). Approximately 85% of BWS cases appear to be sporadic, while 15% of cases are associated with an autosomal dominant inheritance pattern. When a family history is present, the etiology is often due to inherited point mutations in CDKN1C or an unknown cause. The etiology of sporadic cases includes: -Hypomethylation of imprinting center 2 (IC2) (LIT1): approximately 50% to 60% -Paternal uniparental disomy of chromosome 11: approximately 10% to 20% -Hypermethylation of imprinting center 1 (IC1) (H19): approximately 2% to 7% -Unknown: approximately 10% to 20% -Point mutation in CDKN1C: approximately 5% to 10% -Cytogenetic abnormality: approximately 1% to 2% -Differentially methylated region 1 (DMR1) or DMR2 microdeletion: rare The clinical presentation of BWS is dependent on which gene in the 11p15 region is involved. The risk for cancer has been shown to be significantly higher in patients with abnormal methylation of IC1 (H19) versus IC2 (LIT1). In patients with abnormal methylation of IC2 (LIT1), abdominal wall defects and overgrowth are seen at a higher frequency. Russell-Silver syndrome (RSS) is a rare genetic condition with an incidence of approximately 1 in 100,000. RSS is characterized by pre- and postnatal growth retardation with normal head circumference, characteristic facies, fifth finger clinodactyly, and asymmetry of the face, body, and/or limbs. Less commonly observed clinical features include cafe au lait spots, genitourinary anomalies, motor, speech, cognitive delays, and hypoglycemia. Although clinical diagnostic criteria have been developed, it has been demonstrated that many patients with molecularly confirmed RSS do not meet strict clinical diagnostic criteria for RSS. Therefore, most groups recommend a relatively low threshold for considering molecular testing in suspected cases of RSS. RSS is a genetically heterogeneous condition that is associated with genetic and epigenetic alterations at chromosome 7 and the chromosome 11p15.5 region. The majority of cases of RSS are sporadic, although familial cases have been reported. The etiology of sporadic cases of RSS includes: -Hypomethylation of IC1 (H19): approximately 30% to 50% -Maternal uniparental disomy (UPD) of chromosome 7:
approximately 5% to 10%* -11p15.5 duplications: rare -Chromosome 7 duplications: rare* *Note that this test does not detect chromosome 7 UPD. However, testing is available; order UNIPD / Uniparental Disomy. The clinical phenotype of RSS has been associated with the specific underlying molecular etiology. Patients with hypomethylation of IC1 (H19) are more likely to exhibit "classic" RSS phenotype (i.e., severe intrauterine growth retardation, postnatal growth retardation, and asymmetry), while patients with maternal UPD7 often show a milder clinical phenotype. Despite these general genotype-phenotype correlations, many exceptions have been reported. Methylation abnormalities of IC1 (H19) and IC2 (LIT1) can be detected by methyltransferase-sensitive multiple ligation-dependent probe amplification. While testing can determine methylation status, it does not identify the mechanism responsible for the methylation defect (such as paternal uniparental disomy or cytogenetic abnormalities). Hypomethylation of IC2 (LIT1) is hypothesized to silence the expression of a number of maternally expressed genes, including CDKN1C. Hypermethylation of IC1 is hypothesized to silence the expression of H19, while also resulting in overexpression of IGF2. Absence of CDKN1C and H19 expression, in addition to overexpression of IGF2, is postulated to contribute to the clinical phenotype of BWS. Hypomethylation of IC1 is hypothesized to result in overexpression of H19 and underexpression of the IGF2, which is thought to contribute to the clinical phenotype of RSS.

**Useful For:** Confirming a clinical diagnosis of Beckwith-Wiedemann syndrome (BWS) or Russell-Silver syndrome (RSS) Prenatal diagnosis if there is a high suspicion of BWS/RSS based on ultrasound findings or in families at risk for BWS/RSS

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Beech, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust, mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with...
the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<tbody>
<tr>
<td>0</td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
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</tr>
<tr>
<td>2</td>
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</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
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<td>5</td>
<td>50.0-99.9</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Beef IgG**

**Interpretation:** mcg/mL of IgG

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicated immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**Beef Neutral-Regular Insulin, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Beef, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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**FBTRG**  
**Beet Root IgG**

**Interpretation:** mcg/mL of IgG  
Lower Limit of Quantitation 2.0  
Upper Limit of Quantitation 200

**Reference Values:**  
< 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**BEETS**  
**Beets (Beetroot), IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values
   apply to all ages.


### Benzene as Phenol, Occupational Exposure, Urine

**Reference Values:**

- Creatinine: >50 mg/dL
- Phenol: mg/L
- Phenol: mg/G creat

**Normal (unexposed population):**

- less than 10 mg/L

**Exposed:**

- Biological Exposure Index (BEI): 50 mg/g creatinine (End of Shift)

**Toxic:**

- Not Established

### Benzene, Occupational Exposure, Blood

**Reference Values:**

- Units: mg/L

**Normal (unexposed population):**

- None detected

**Exposed (end-of-shift):**

- Blood benzene concentrations of greater than 0.1 mg/L correlate with exposure to greater than 10 ppm benzene in air.

**Toxic:**

- Blood benzene concentrations greater than 0.90 mg/L have been observed in fatal cases of benzene exposure.

### Benzodiazepines Confirmation, Chain of Custody, Urine

**Clinical Information:** Benzodiazepines are a group of compounds having a common molecular structure and acting similarly as depressants of the central nervous system. As a class of drugs, benzodiazepines are among the most commonly prescribed drugs in the western hemisphere because of their efficacy, safety, low addiction potential, minimal side effects, and high public demand for sedative and anxiolytic agents. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detecting drug use involving benzodiazepines such as alprazolam, flunitrazepam, chlordiazepoxide, diazepam, flurazepam, lorazepam, and triazolam Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the...
individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** Benzodiazepines are extensively metabolized, and the parent compounds are not detected in urine. This test screens for (and confirms) the presence of: -Nordiazepam, oxazepam (metabolites of chlordiazepoxide) -Nordiazepam, oxazepam and temazepam (metabolites of diazepam) -Lorazepam -Hydroxyethylfluorazepam (metabolite of flurazepam) -Alpha hydroxyalprazolam (metabolite of alprazolam) -Alpha hydroxytriazolam (metabolite of triazolam) -7-Aminoclonazepam (metabolite of clonazepam) -7-Aminoflunitrazepam (metabolite of flunitrazepam) The clearance half-life of long-acting benzodiazepines is >24 hours. It takes 5 to 7 half-lives to clear 98% of a drug dose.

Therefore, the presence of a long-acting benzodiazepine greater than the limit of quantification indicates exposure within a 5- to 20-day interval preceding specimen collection. Following a dose of diazepam, the drug and its metabolites appear in the urine within 30 minutes. Peak urine output is reached between 1 and 8 hours. See Mayo Medical Laboratories Drugs of Abuse Testing Guide at http://www.mayomedicallaboratories.com/test-info/drug-book/index.html for additional information including metabolism, clearance (half-life), and approximate detection times.

**Reference Values:**
Negative
Cutoff concentrations:

**IMMUNOASSAY SCREEN**
<100 ng/mL

**NORDIAZEPAM BY GC-MS**
<100 ng/mL

**OXAZEPAM BY GC-MS**
<100 ng/mL

**LORAZEPAM BY GC-MS**
<100 ng/mL

**TEMAZEPAM BY GC-MS**
<100 ng/mL

**OH-ETHYL-FLURAZEPAM BY GC-MS**
<100 ng/mL

**7-NH-CLONAZEPAM BY GC-MS**
<100 ng/mL

**ALPHA OH-ALPRAZOLAM BY GC-MS**
<100 ng/mL

**7-NH-FLUNITRAZEPAM BY GC-MS**
<50 ng/mL

**ALPHA OH-TRIAZOLAM BY GC-MS**
<100 ng/mL

Benzodiazepines Confirmation, Urine

Clinical Information: Benzodiazepines are any of a group of compounds having a common molecular structure and acting similarly as depressants of the central nervous system. As a class of drugs, benzodiazepines are among the most commonly prescribed drugs in the western hemisphere because of their efficacy, safety, low addiction potential, minimal side effects, and high public demand for sedative and anxiolytic agents.

Useful For: Detecting drug use involving benzodiazepines such as alprazolam, flunitrazepam, chlordiazepoxide, diazepam, flurazepam, lorazepam, and triazolam

Interpretation: Benzodiazepines are extensively metabolized, and the parent compounds are not detected in urine. This test screens for (and confirms) the presence of: -Nordiazepam, oxazepam (metabolites of chlordiazepoxide) -Nordiazepam, oxazepam and temazepam (metabolites of diazepam) -Lorazepam -Hydroxyethylfluorazepam (metabolite of flurazepam) -Alpha hydroxyalprazolam (metabolite of alprazolam) -Alpha hydroxytriazolam (metabolite of triazolam) -7-aminoclonazepam (metabolite of clonazepam) -7-aminoflunitrazepam (metabolite of flunitrazepam) The clearance half-life of long-acting benzodiazepines is more than 24 hours. It takes 5 to 7 half-lives to clear 98% of a drug dose. Therefore, the presence of a long-acting benzodiazepine greater than the limit of quantification indicates exposure within a 5 to 20-day interval preceding specimen collection. Following a dose of diazepam, the drug and its metabolites appear in the urine within 30 minutes. Peak urine output is reached between 1 and 8 hours. See Mayo Medical Laboratories Drugs of Abuse Testing Guide at http://www.mayomedicallaboratories.com/test-info/drug-book/index.html for additional information including metabolism, clearance (half-life), and approximate detection times.

Reference Values:
Negative

Cutoff concentrations:
NORDIAZEPAM BY GC-MS
<100 ng/mL

OXAZEPAM BY GC-MS
<100 ng/mL

LORAZEPAM BY GC-MS
<100 ng/mL

TEMAZEPAM BY GC-MS
<100 ng/mL

OH-ETHYL-FLURAZEPAM BY GC-MS
<100 ng/mL

7-NH-CLONAZEPAM BY GC-MS
<100 ng/mL

ALPHA OH-ALPRAZOLAM BY GC-MS
<100 ng/mL

7-NH-FLUNITRAZEPAM BY GC-MS
<50 ng/mL

ALPHA OH-TRIAZOLAM BY GC-MS
<100 ng/mL

Benztropine (Cogentin), Serum

**Reference Values:**
Reference Range: 5.0 - 25.0 ng/mL

Ber-EP4 (Epithelial Cell Adhesion Molecule/EPCAM) Immunostain, Technical Component Only

**Clinical Information:** Epithelial cell adhesion molecule/EPCAM (Ber-EP4) is expressed on most epithelial cells of the body, with the exception of squamous epithelium and mesothelium. It has been used to distinguish basal cell carcinoma from squamous cell carcinoma of the skin, and to distinguish pulmonary adenocarcinoma from mesothelioma.

**Useful For:** Aids in distinguishing basal cell carcinoma from squamous cell carcinoma of the skin Aids in distinguishing pulmonary adenocarcinoma from mesothelioma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

Berlin Beetle, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of
allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Bermuda Grass, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
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<td>0</td>
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<tr>
<td>2</td>
<td>0.70-3.49</td>
</tr>
</tbody>
</table>

**FBERY** 91092  
**Beryllium, Blood**  
**Reference Values:**  
Reference Range: <1.0 ng/mL

**WBSEQ** 62128  
**Beta Globin Gene Sequencing, Blood**  
**Clinical Information:** Beta globin gene sequencing is useful in the evaluation of beta globin chain variants and beta thalassemia. It detects almost all beta globin variants and the most common beta thalassemia mutations, although prevalence is ethnicity-dependent. Because these conditions are often complex, this test should always be interpreted in the context of protein studies, such as hemoglobin electrophoresis and RBC indices. The majority of beta globin chain variants are clinically and hematologically benign; however, some have important clinical consequences, such as erythrocytosis, cyanosis/hypoxia, chronic hemolysis, or unexplained microcytosis. Most of the common clinically significant hemoglobin (Hb) variants (ie, Hb S, Hb C, Hb E, and others) are easily distinguished by hemoglobin electrophoresis and do not require molecular analysis. In addition, they are frequently found in complex hemoglobin disorders due to multiple mutations, and accurate classification requires sequencing data within the context of protein data. In some instances, beta globin sequencing is necessary to identify or confirm the identity of rare variants, especially those associated with erythrocytosis and chronic hemolytic anemia. Rare hyperunstable variants (also termed dominant beta thalassemia mutations) result in hemolytic anemia and do not create protein stable enough to be detectable by protein methods, including stability studies. They are not always associated with elevated Hb A2 or microcytosis and, therefore, can be electrophoretically silent. These require a high degree of clinical suspicion as all electrophoretic testing as well as stability studies cannot exclude this condition. Beta thalassemia is an autosomal recessive condition characterized by decreased or absent synthesis of beta globin chains due to mutations in the beta globin gene (HBB). No abnormal protein is present and diagnosis by electrophoresis relies on hemoglobin fraction percentage alterations (ie, Hb A2 or Hb F elevations). Beta thalassemia can be split into 3 broad classes (categorized by clinical features) 1. Beta thalassemia trait (also called beta thalassemia minor and beta thalassemia carrier) (B[A]B[+] or B[A]B[0]). 2. Beta thalassemia intermedia (B[+]B[+] or B[+]B[0]) 3. Beta thalassemia major (B[+]B[0] or B[0]B[0]) Beta thalassemia trait is typically a harmless condition with varying degrees of microcytosis and hypochromia and sometimes mild anemia. Transfusions are not required. Beta thalassemia intermedia is a clinical distinction and is characterized by a more severe degree of anemia than beta thalassemia trait with few or intermittent transfusions required. Later in life, these individuals are at risk for iron overload even in the absence of chronic transfusion due to increased intestinal absorption of iron. Beta thalassemia major typically comes to medical attention early in life due to severe anemia, hepatosplenomegaly, and failure to thrive. Skeletal changes are also common due to expansion of the bone marrow. Without appropriate treatment these patients have a shortened lifespan. The majority of beta thalassemia mutations (>90%) are point mutations, small deletions, or insertions, which are detected by beta globin gene sequencing. The remaining beta thalassemia mutations are either due to large genomic deletions of HBB or, very rarely, trans-acting beta thalassemia mutations located outside of the beta globin gene cluster. Some rare beta chain variants can be clinically or electrophoretically indistinguishable from beta thalassemia and cannot be confirmed without molecular analysis.
Useful For: Diagnosis of beta thalassemia intermedia or major Identification of a specific beta thalassemia mutation (ie, unusually severe beta thalassemia trait) Evaluation of an abnormal hemoglobin electrophoresis identifying a rare beta globin variant Evaluation of chronic hemolytic anemia of unknown etiology Evaluation of hereditary erythrocytosis with left-shifted p50 oxygen dissociation results Preconception screening when there is a concern for a beta hemoglobin disorder based on family history

Interpretation: The alteration will be provided with the classification, if known. Further interpretation requires correlation with protein studies and RBC indices.

Reference Values: An interpretive report will be provided.


FBLGG 57667

Beta Lactoglobulin IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values: <2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

AB2GP 86180

Beta-2 Glycoprotein 1 Antibodies, IgA, Serum

Clinical Information: Beta-2 glycoprotein 1 (beta-2 GP1, also called apolipoprotein H) is a 326-amino acid polypeptide synthesized by hepatocytes, endothelial cells and trophoblast cells. It contains 5 homologous domains of approximately 60 amino acids each.(1,2) Domain 5, located at the C terminus, contains a hydrophobic core surrounded by 14 positively charged amino acid residues that promote electrostatic interactions with plasma membranes via interactions with negatively charged phospholipids. Complexes of beta-2 GP1 and phospholipid in vivo reveal epitopes that react with natural autoantibodies.(3) Plasma from normal individuals contains low concentrations of IgG autoantibodies to beta-2 GP1 antibodies that are of moderate affinity and react with an epitope on the first domain near the N terminus. Pathologic levels of beta-2 GP1 antibodies occur in patients with antiphospholipid syndrome (APS). APS is associated with a variety of clinical symptoms notably thrombosis, pregnancy complications, unexplained cutaneous circulatory disturbances (livido reticularis or pyoderma gangrenosum), thrombocytopenia or hemolytic anemia, and nonbacterial thrombotic endocarditis. Beta-2 GP1 antibodies are found with increased frequency in patients with systemic rheumatic diseases, especially systemic lupus erythematosus. Autoantibodies to beta-2 GP1 antibodies are detected in the clinical laboratory by different types of assays including immunoassays and functional coagulation assays. Immunoassays for beta-2 GP1 antibodies can be performed using either a composite substrate comprised of beta-2 GP1 plus anionic phospholipid (eg, cardiolipin or phosphatidylserine), or beta-2 GP1 alone. Antibodies detected by immunoassays that utilize composite
substrates are commonly referred to as phospholipid or cardiolipin antibodies. Antibodies detected using beta-2 GP1 substrate without phospholipid (so called direct assays) are referred to simply as "beta-2 GP1 antibodies." Some beta-2 GP1 antibodies are capable of inhibiting clot formation in functional coagulation assays that contain low concentrations of phospholipid cofactors. Antibodies detected by functional coagulation assays are commonly referred to as lupus anticoagulants. The diagnosis of APS requires at least 1 clinical criteria and 1 laboratory criteria be met.(5) The clinical criteria include vascular thrombosis (arterial or venous in any organ or tissue) and pregnancy morbidity (unexplained fetal death, premature birth, severe preeclampsia, or placental insufficiency). Other clinical manifestations, including heart valve disease, livedo reticularis, thrombocytopenia, nephropathy, neurological symptoms, are often associated with APS, but are not included in the diagnostic criteria. The laboratory criteria for diagnosis of APS are the presence of lupus anticoagulant, the presence of IgG and/or IgM anticardiolipin antibody (>40 GPL, >40 MPL or >99th percentile), and/or the presence of IgG and/or IgM beta-2 GP1 antibody (>99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks. Direct assays for beta-2GP 1 antibodies have been reported to be somewhat more specific (but less sensitive) for disease diagnosis in patients with APS.(4) Anticardiolipin and beta-2 GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity.

Useful For: Evaluation of patients with suspected antiphospholipid syndrome by identification of beta-2 GP1 IgA antibodies

Interpretation: Strongly positive results for IgG and IgM beta-2 glycoprotein 1 (beta-2 GP1) antibodies (>40 U/mL for IgG and/or IgM) are diagnostic criterion for antiphospholipid syndrome (APS). Lesser levels of beta-2 GP1 antibodies and antibodies of the IgA isotype may occur in patients with clinical signs of APS, but the results are not considered diagnostic. Beta-2 GP1 antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. IgA beta-2 GP1 antibody result >15 U/mL with negative IgG and IgM beta-2 GP1 antibody results are not diagnostic for APS. Detection of beta-2 GP1 antibodies is not affected by anticoagulant treatment.

Reference Values:
<15.0 U/mL (negative)
15.0-39.9 U/mL (weakly positive)
40.0-79.9 U/mL (positive)
> or =80.0 U/mL (strongly positive)
Results are expressed in arbitrary units.
Reference values apply to all ages.


B2GMG Beta-2 Glycoprotein 1 Antibodies, IgG and IgM, Serum

Clinical Information: Beta-2 glycoprotein 1 (beta-2 GP1, also called apolipoprotein H) is a 326-amino acid polypeptide synthesized by hepatocytes, endothelial cells, and trophoblast cells. It contains 5 homologous domains of approximately 60 amino acids each.(1,2) Domain 5, located at the C terminus, contains a hydrophobic core surrounded by 14 positively charged amino acid residues that promote electrostatic interactions with plasma membranes via interactions with negatively charged phospholipids. Complexes of beta-2 GP1 and phospholipids in vivo reveal epitopes that react with natural autoantibodies.(3) Plasma from normal individuals contains low concentrations of IgG autoantibodies to beta-2 GP1 (beta-2 GP1 antibodies) that are of moderate affinity and react with an epitope on the first
domain near the N terminus. Pathologic levels of beta-2 GP1 antibodies occur in patients with antiphospholipid syndrome (APS). APS is associated with a variety of clinical symptoms, notably, thrombosis, pregnancy complications, unexplained cutaneous circulatory disturbances (livido reticularis or pyoderma gangrenosum), thrombocytopenia or hemolytic anemia, and nonbacterial thrombotic endocarditis. Beta-2 GP1 antibodies are found with increased frequency in patients with systemic rheumatic diseases, especially systemic lupus erythematosus. Beta-2 GP1 antibodies are detected in the clinical laboratory by different types of assays including immunoassays and functional coagulation assays. Immunoassays for beta-2 GP1 antibodies can be performed using either a composite substrate comprised of beta-2 GP1 plus anionic phospholipid (eg, cardiolipin or phosphatidylserine), or beta-2 GP1 alone. Antibodies detected by immunoassays that utilize composite substrates are commonly referred to as phospholipid or cardiolipin antibodies. Antibodies detected using beta-2 GP1 substrate without phospholipid (so-called direct assays) are referred to simply as beta-2 GP1 antibodies. Some beta-2 GP1 antibodies are capable of inhibiting clot formation in functional coagulation assays that contain low concentrations of phospholipid cofactors. Antibodies detected by functional coagulation assays are commonly referred to as lupus anticoagulants. The diagnosis of APS requires at least 1 clinical criteria and 1 laboratory criteria be met.(5) The clinical criteria include vascular thrombosis (arterial or venous in any organ or tissue) and pregnancy morbidity (unexplained fetal death, premature birth, severe preeclampsia, or placental insufficiency). Other clinical manifestations, including heart valve disease, livedo reticularis, thrombocytopenia, nephropathy, neurological symptoms, are often associated with APS but are not included in the diagnostic criteria. The laboratory criteria for diagnosis of APS are the presence of lupus anticoagulant, the presence of IgG and/or IgM anticardiolipin antibody (>40 GPL, >40 MPL, or >99th percentile), and/or the presence of IgG and/or IgM beta-2 GP1 antibody (>99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks. Direct assays for beta-2 GP1 antibodies have been reported to be somewhat more specific (but less sensitive) for disease diagnosis in patients with APS.(4) Anticardiolipin and beta-2 GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity.

**Useful For:** Evaluation of patients with suspected antiphospholipid syndrome by identification of beta-2 GP1 IgG and IgM antibodies

**Interpretation:** Strongly positive results for beta-2 glycoprotein 1 (beta-2 GP1) antibodies (>40 U/mL for IgG and/or IgM) are diagnostic criterion for APS. Lesser levels of beta-2 GP1 antibodies and antibodies of the IgA isotype may occur in patients with clinical signs of antiphospholipid syndrome (APS), but the results are not considered diagnostic. Beta-2 GP1 antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. Detection of beta-2 GP1 antibodies is not affected by anticoagulant treatment.

**Reference Values:**

- <15.0 U/mL (negative)
- 15.0-39.9 U/mL (weakly positive)
- 40.0-79.9 U/mL (positive)
- > or =80.0 U/mL (strongly positive)

Results are expressed in arbitrary units and apply to IgG and IgM values. Reference values apply to all ages.

**Clinical References:**


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**GB2GP**

**Beta-2 Glycoprotein 1 Antibodies, IgG, Serum**

86182

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 287
Clinical Information: Beta-2 glycoprotein 1 (beta-2 GP1, also called apolipoprotein H) is a 326-amino acid polypeptide synthesized by hepatocytes, endothelial cells, and trophoblast cells. It contains 5 homologous domains of approximately 60 amino acids each. Domain 5, located at the C terminus, contains a hydrophobic core surrounded by 14 positively charged amino acid residues that promote electrostatic interactions with plasma membranes via interactions with negatively charged phospholipids. Complexes of beta 2 GP1 and phospholipid in vivo reveal epitopes that react with natural autoantibodies. Plasma from normal individuals contains low concentrations of IgG autoantibodies to beta-2 GP1 (beta-2 GP1 antibodies) that are of moderate affinity and react with an epitope on the first domain near the N terminus. Pathologic levels of beta 2 GP1 antibodies occur in patients with antiphospholipid syndrome (APS). APS is associated with a variety of clinical symptoms notably thrombosis, pregnancy complications, unexplained cutaneous circulatory disturbances (livido reticularis or pyoderma gangrenosum), thrombocytopenia or hemolytic anemia, and nonbacterial thrombotic endocarditis. Beta 2 GP1 antibodies are found with increased frequency in patients with systemic rheumatic diseases, especially systemic lupus erythematosus. Autoantibodies to beta-2 GP1 are detected in the clinical laboratory by different types of assays including immunoassays and functional coagulation assays. Immunoassays for beta-2 GP1 antibodies can be performed using either a composite substrate comprised of beta-2 GP1 plus anionic phospholipid (eg, cardiolipin or phosphatidylserine), or beta-2 GP1 alone. Antibodies detected by immunoassays that utilize composite substrates are commonly referred to as phospholipid or cardiolipin antibodies. Antibodies detected using beta-2 GP1 substrate without phospholipid (so-called direct assays) are referred to simply as "beta-2 GP1 antibodies." Some beta-2 GP1 antibodies are capable of inhibiting clot formation in functional coagulation assays that contain low concentrations of phospholipid cofactors. Antibodies detected by functional coagulation assays are commonly referred to as lupus anticoagulants. The diagnosis of APS requires at least 1 clinical criteria and 1 laboratory criteria be met. The clinical criteria include vascular thrombosis (arterial or venous in any organ or tissue) and pregnancy morbidity (unexplained fetal death, premature birth, severe preeclampsia, or placental insufficiency). Other clinical manifestations, including heart valve disease, livedo reticularis, thrombocytopenia, nephropathy, neurological symptoms, are often associated with APS but are not included in the diagnostic criteria. The laboratory criteria for diagnosis of APS are the presence of lupus anticoagulant, the presence of IgG and/or IgM anticardiolipin antibody (>40 GPL, >MPL or >99th percentile), and/or the presence of IgG and/or IgM beta GP1 antibody (>99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks. Direct assays for beta-2 GP1 antibodies have been reported to be somewhat more specific (but less sensitive) for disease diagnosis in patients with APS. Anticardiolipin and beta-2 GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity.

Useful For: Evaluation of patients with suspected antiphospholipid syndrome by identification of beta-2 GP1 IgG antibodies

Interpretation: Strongly positive results for beta 2 glycoprotein 1 (beta 2 GP1) antibodies (>40 U/mL for IgG and/or IgM) are diagnostic criterion for antiphospholipid syndrome (APS). Lesser levels of IgG and IgM beta 2 GP1 antibodies and antibodies of the IgA isotype may occur in patients with clinical signs of APS, but the results are not considered diagnostic. Beta 2 GP1 antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. Detection of beta 2 GP1 antibodies is not affected by anticoagulant treatment.

Reference Values:
<15.0 U/mL (negative)
15.0-39.9 U/mL (weakly positive)
40.0-79.9 U/mL (positive)
> or =80.0 U/mL (strongly positive)
Results are expressed in arbitrary units.
Reference values apply to all ages.

Beta-2 Glycoprotein 1 Antibodies, IgM, Serum

**Clinical Information:** Beta-2 glycoprotein 1 (beta-2 GPI, also called apolipoprotein H) is a 326-amino acid polypeptide synthesized by hepatocytes, endothelial cells, and trophoblast cells. It contains 5 homologous domains of approximately 60 amino acids each. Domain 5, located at the C terminus, contains a hydrophobic core surrounded by 14 positively charged amino acid residues that promote electrostatic interactions with plasma membranes via interactions with negatively charged phospholipids. Complexes of beta 2 GP1 and phospholipid in vivo reveal epitopes that react with natural autoantibodies. Plasma from normal individuals contains low concentrations of IgG autoantibodies to beta-2 GP1 (beta-2 GP1 antibodies) that are of moderate affinity and react with an epitope on the first domain near the N terminus. Pathologic levels of beta 2 GP1 antibodies occur in patients with antiphospholipid syndrome (APS). APS is associated with a variety of clinical symptoms, notably, thrombosis, pregnancy complications, unexplained cutaneous circulatory disturbances (livido reticularis or pyoderma gangrenosum), thrombocytopenia or hemolytic anemia, and nonbacterial thrombotic endocarditis. Beta 2 GP1 antibodies are found with increased frequency in patients with systemic rheumatic diseases, especially systemic lupus erythematosus. Autoantibodies to beta-2 GP1 antibodies are detected in the clinical laboratory by different types of assays including immunoassays and functional coagulation assays. Immunoassays for beta-2 GP1 antibodies can be performed using either a composite substrate comprised of beta-2 GP1 plus anionic phospholipid (eg, cardiolipin or phosphatidylserine), or beta-2 GP1 alone. Antibodies detected by immunoassays that utilize composite substrates are commonly referred to as phospholipid or cardiolipin antibodies. Antibodies detected using beta-2 GP1 substrate without phospholipid (so called direct assays) are referred to simply as "beta-2 GP1 antibodies." Some beta-2 GP1 antibodies are capable of inhibiting clot formation in functional coagulation assays that contain low concentrations of phospholipid cofactors. Antibodies detected by functional coagulation assays are commonly referred to as lupus anticoagulants. The diagnosis of APS requires at least 1 clinical criteria and 1 laboratory criteria be met. The clinical criteria include vascular thrombosis (arterial or venous in any organ or tissue) and pregnancy morbidity (unexplained fetal death, premature birth, severe preeclampsia, or placental insufficiency). Other clinical manifestations, including heart valve disease, livedo reticularis, thrombocytopenia, nephropathy, neurological symptoms, are often associated with APS but are not included in the diagnostic criteria. The laboratory criteria for diagnosis of APS are the presence of lupus anticoagulant, the presence of IgG and/or IgM antiscardiolipin antibody (>40 GPL, >40 MPL or >99th percentile), and/or the presence of IgG and/or IgM beta-2 GP1 antibody (>99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks. Direct assays for beta 2 GP1 antibodies have been reported to be somewhat more specific (but less sensitive) for disease diagnosis in patients with APS. Anticardiolipin and beta 2 GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity.

**Useful For:** Evaluation of patients with suspected antiphospholipid syndrome by identification of beta-2 GP1 IgM antibodies

**Interpretation:** Strongly positive results for beta-2 glycoprotein 1 (beta-2 GPI) antibodies (>40 U/mL for IgG and/or IgM) are diagnostic criterion for antiphospholipid syndrome (APS). Lesser levels of beta-2 GP1 antibodies and antibodies of the IgA isotype may occur in patients with clinical signs of APS, but the results are not considered diagnostic. Beta-2 GPI antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. Detection of beta-2 GP1 antibodies is not affected by anticoagulant treatment.

**Reference Values:**
- <15.0 U/mL (negative)
- 15.0-39.9 U/mL (weakly positive)
- 40.0-79.9 U/mL (positive)
- > or =80.0 U/mL (strongly positive)
Results are expressed in arbitrary units. Reference values apply to all ages.


**Beta-2 Microglobulin (B2M), Urine**

**Clinical Information:** Beta-2 microglobulin is a low-molecular-weight protein that forms the light chain component of class I histocompatibility (HLA: human leukocyte antigen) antigens. Increased urine levels are seen in proximal tubular renal damage due to a variety of causes, including cadmium, mercury, lithium, or aminoglycoside toxicity; pyelonephritis; and Balkan nephropathy, a chronic interstitial nephritis of unknown etiology.

**Useful For:** Evaluation of renal tubular damage Monitoring exposure to cadmium and mercury

**Interpretation:** Increased excretion is consistent with renal tubular damage. Beta-2 microglobulin excretion is increased 100 to 1,000 times normal levels in cadmium-exposed workers.

**Reference Values:**
< or =300 mcg/L


**Beta-2 Transferrin: Detection of Spinal Fluid in Other Body Fluid**

**Clinical Information:** The diagnosis of cerebrospinal fluid (CSF) rhinorrhea or otorrhea (leakage of CSF into the nose or ear canal, usually as a result of head trauma, tumor, congenital malformation, or surgery) is often difficult to confirm. Traditional chemical analyses (eg, glucose, protein, specific gravity) are unreliable. Radiographic studies, especially those involving the injection of dyes or radiographic compounds, are costly and may introduce additional risks to the patient. Transferrin that migrates in the beta-1 electrophoretic fraction (beta-1 transferrin) is found in most body fluids. Beta-2 transferrin is a CSF-specific variant of transferrin and is used as an endogenous marker of CSF leakage. Beta-2 transferrin is formed by loss of sialic acid due to the presence of neuraminidase in the central nervous system. Beta-2 transferrin has also been called CSF-specific transferrin and tau protein. Prompt diagnosis and localization facilitates appropriate decisions and decreases the risk of meningitis.

**Useful For:** Detection of spinal fluid in body fluids, such as ear or nasal fluid

**Interpretation:** The cerebrospinal fluid (CSF) variant of transferrin is identified by its unique electrophoretic migration. If beta-1 and beta-2 transferrin are detected in drainage fluids, the specimen is presumed to be contaminated with CSF. The presence of beta-2 transferrin band is detectable with as little as 2.5% spinal fluid contamination of body fluids.
Reference Values:
Negative, no beta-2 transferrin (spinal fluid) detected


**Beta-2-Microglobulin (Beta-2-M), Serum**

**Clinical Information:** Beta-2-microglobulin (beta-2-M) is a small membrane protein (11,800 Dalton) associated with the heavy chains of class I major histocompatibility complex proteins and is, therefore, on the surface of all nucleated cells. The small size allows beta-2-M to pass through the glomerular membrane, but it is almost completely reabsorbed in the proximal tubules. Serum beta-2-M levels are elevated in diseases associated with increased cell turnover. Levels are also elevated in several benign conditions such as chronic inflammation, liver disease, renal dysfunction, some acute viral infections, and a number of malignancies, especially hematologic malignancies associated with the B-lymphocyte lineage. In multiple myeloma, beta-2-M is a powerful prognostic factor and values <4 mcg/mL are considered a good prognostic factor. In renal tubular disease, serum levels are low and urine levels are high. Although urine beta-2-M has been used to assess tubular dysfunction, it is not stable in urine below pH 5.5. See Laboratory Screening Tests for Suspected Multiple Myeloma in Special Instructions.

**Useful For:** Prognosis assessment of multiple myeloma Evaluation of renal tubular disorders

**Interpretation:** Serum beta-2-microglobulin (beta-2-M) <4 mcg/mL is a good prognostic factor in patients with multiple myeloma. In a study of pretreatment serum beta-2-M levels in 100 patients with myeloma it was reported that the median survival of patients with values >4 mcg/mL was 12 months, whereas median survival for patients with values <4 mcg/mL was 43 months.

**Reference Values:**
1.21-2.70 mcg/mL


**Beta-2-Microglobulin (Beta-2-M), Spinal Fluid**

**Clinical Information:** Beta-2-microglobulin (BETA-2-M) is a small membrane protein (11,800 Dalton) associated with the heavy chains of class I major histocompatibility complex proteins and is, therefore, on the surface of all nucleated cells. The small size allows BETA-2-M to pass through the glomerular membrane, but it is almost completely reabsorbed in the proximal tubules. Increased BETA-2-M levels in the cerebrospinal fluid (CSF) have been shown to be of diagnostic use in non-Hodgkin lymphoma with central nervous system involvement. Elevated CSF:serum ratios seen in patients with aseptic meningo-encephalitis suggest the possibility of neurologic processes including those associated with HIV infection and acute lymphoblastic leukemia. BETA-2-M measurement in multiple sclerosis seems to be of indeterminate usefulness.

**Useful For:** Evaluation of central nervous system inflammation and B-cell proliferative diseases
**Interpretation:** Elevations of cerebrospinal fluid beta-2-microglobulin levels may be seen in a number of diseases including malignancies, autoimmune disease, and neurological disorders.

**Reference Values:**
0.70-1.80 mcg/mL

**Clinical References:**

**Beta-Amyloid Immunostain, Technical Component Only**

**Clinical Information:** Beta-amyloid (Abeta) peptide deposition is a major pathological feature of Alzheimer disease. Abeta peptides are proteolytic fragments of the amyloid precursor protein that aggregate and form extracellular amyloid plaques.

**Useful For:** Identification of senile plaques in neurodegenerative disease

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Beta-Catenin (CTNNB1) Mutation Analysis, Tumor**

**Clinical Information:** Desmoid-type fibromatosis is a locally invasive soft tissue tumor. The histological diagnosis of desmoid-type fibromatosis is challenging. Mutations in exon 3 of the beta-catenin (BCAT also known as CTNNB1) gene have been identified in 50% to 87% of desmoid-type fibromatosis, including T41A (121 A->G), S45P (133 T->C), and S45F (134 C->T), but not in other soft...
tissue tumors. Patients harboring beta-catenin mutations may have a higher recurrence rate compared to the patients with wild-type beta-catenin. Next-generation sequencing has recently emerged as an accurate, cost-effective method to identify alterations across numerous genes. This test uses formalin-fixed paraffin-embedded tissue or cytology slides to assess for common somatic mutations in the beta-catenin gene known to be associated with desmoid-type fibromatosis. The results of this test can be useful for supporting a diagnosis of desmoid-type fibromatosis and predicting prognosis.

**Useful For:** Distinguishing desmoid-type fibromatosis from other soft tissue tumors by assessing gene targets with in the BCAT (CTNNB1) gene

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

### BCATN 70361

**Beta-Catenin Immunostain, Technical Component Only**

**Clinical Information:** Beta-catenin is involved in cellular cohesion through binding to the cytoplasmic tail of E-cadherin, and in intracellular signaling as a component of the Wnt pathway. In normal cells, B-catenin levels are regulated by the adenomatous polyposis coli (APC) protein, which promotes normal degradation of the protein. Mutations in either B-catenin or APC can result in accumulation of the protein and abnormal localization in the nucleus. In the nucleus, B-catenin acts as a cofactor in the upregulation of oncogenes including cyclin D1 and cmyc. In normal tissues, staining for B-catenin is limited to the membrane. Aberrant nuclear staining can be used diagnostically in selected tumors of the soft tissue (fibromatoses, endometrial stromal sarcoma), pancreas, liver and lung.

**Useful For:** Identification of aberrant nuclear staining pattern observed in some tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

### CTX 83175

**Beta-CrossLaps (Beta-CTx), Serum**

**Clinical Information:** Human bone is continuously remodeled through a process of bone formation and resorption. Approximately 90% of the organic matrix of bone is type I collagen, a helical protein that is crosslinked at the N- and C-terminal ends of the molecule. During bone resorption, osteoclasts
secrete a mixture of acid and neutral proteases that degrade the collagen fibrils into molecular fragments including C-terminal telopeptide (CTx). As bone ages, the alpha form of aspartic acid present in CTx converts to the beta form (beta-CTx). Beta-CTx is released into the bloodstream during bone resorption and serves as a specific marker for the degradation of mature type I collagen. Elevated serum concentrations of beta-CTx have been reported in patients with increased bone resorption. Bone turnover markers are physiologically elevated during childhood, growth, and fracture healing. The elevations in bone resorption markers and bone formation markers are typically balanced in these circumstances and are of no diagnostic value. By contrast, bone turnover markers may be useful when the bone remodeling process is unbalanced. Abnormalities in the process of bone remodeling can result in changes in skeletal mass and shape. Many diseases, in particular hyperthyroidism, all forms of hyperparathyroidism, most forms of osteomalacia and rickets (even if not associated with hyperparathyroidism), hypercalcemia of malignancy, Paget disease, multiple myeloma, and bone metastases, as well as various congenital diseases of bone formation and remodeling, can result in accelerated and unbalanced bone turnover. Unbalanced bone turnover is also found in age-related and postmenopausal osteopenia and osteoporosis. Disease-associated bone turnover abnormalities should normalize in response to effective therapeutic interventions, which can be monitored by measurement of serum and urine bone resorption markers.

**Useful For:** An aid in monitoring antiresorptive therapies (eg, bisphosphonates and hormone replacement therapy) in postmenopausal women treated for osteoporosis and individuals diagnosed with osteopenia An adjunct in the diagnosis of medical conditions associated with increased bone turnover

**Interpretation:** Elevated levels of beta-C-terminal telopeptide (CTx) indicate increased bone resorption. Increased levels are associated with osteoporosis, osteopenia, Paget disease, hyperthyroidism, and hyperparathyroidism. In patients taking antiresorptive agents (bisphosphonates or hormone replacement therapy), a decrease of 25% or more from baseline beta-CTx levels (ie, prior to the start of therapy) 3 to 6 months after initiation of therapy indicates an adequate therapeutic response.

**Reference Values:**

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<th>Reference Range</th>
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<tr>
<td></td>
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</table>

**Clinical References:**

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**Beta-Galactosidase, Blood**

**Clinical Information:** Beta-galactosidase is a lysosomal enzyme responsible for catalyzing the hydrolysis of gangliosides. The deficiency of this enzyme can be seen in the following conditions: GM1 gangliosidosis, Morquio syndrome B, and galactosialidosis. Enzymatic testing is not reliable for carrier detection of these conditions. GM1 gangliosidosis is an autosomal recessive lysosomal storage disorder caused by reduced or absent beta-galactosidase activity. Absent or reduced activity leads to the accumulation of GM1 gangliosides, oligosaccharides, and keratan sulfate. The disorder can be classified into 3 subtypes that vary with regard to age of onset and clinical presentation. Type 1, or infantile onset, typically presents between birth and 6 months with a very rapid progression of hypotonia, dysostosis
multiplex, hepatosplenomegaly, central nervous system degeneration, and death usually by 1 to 2 years. Type 2 is generally classified as late infantile or juvenile with onset between 7 months and 3 years presenting with developmental delays and a slower progression. Type 3 is an adult or chronic variant with onset between 3 and 30 years and is typically characterized by slowly progressive dementia with Parkinsonian features and dystonia. The incidence has been estimated to be 1 in 100,000 to 200,000 live births. Mucopolysaccharidosis type IVB (MPS IVB, Morquio B) is an autosomal recessive lysosomal storage disorder caused by reduced or absent beta-galactosidase activity. The mucopolysaccharidoses are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans; GAGs). Accumulation of GAGs (also known as mucopolysaccharides) in lysosomes interferes with normal functioning of cells, tissues, and organs. MPS IVB is caused by a reduced or absent activity of the beta-galactosidase enzyme and gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms of MPS IVB are widely variable ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, hepatosplenomegaly, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. Galactosialidosis is an autosomal recessive lysosomal storage disease associated with a combined deficiency of beta-galactosidase and neuraminidase secondary to a defect in the cathepsin A protein. The disorder can be classified into 3 subtypes that vary with regard to age of onset and clinical presentation. Typical clinical presentation is coarse facial features, cherry-red spots, and skeletal dysplasia. The early infantile form is associated with fetal hydrops, skeletal dysplasia, and early death. The late infantile form typically presents with short stature dystosis multiplex, coarse facial features, corneal clouding, hepatosplenomegaly, and/or heart valve problems. The juvenile/adult form is typically characterized by progressive neurologic degeneration, ataxia, and angiodysplasias. The incidence of the juvenile/adult form is greater in individuals with Japanese ancestry. Patients with mucolipidosis II/III (I-cell disease) may also demonstrate deficiency of beta-galactosidase in leukocytes, in addition to deficiency of other hydrolases. I-cell disease is an autosomal recessive lysosomal storage disorder resulting in impaired transport and phosphorylation of newly synthesized lysosomal proteins to the lysosome due to deficiency of N-acetylglucosamine 1-phosphotransferase (GlcNAc). Characteristic clinical features include short stature, skeletal and cardiac abnormalities, and developmental delay. Measurement of beta-galactosidase activity is not the preferred diagnostic test for I-cell disease but may be included in the testing strategy. A diagnostic workup in an individual with GM1 gangliosidosis, Morquio B, or galactosialidosis typically demonstrates decreased beta-galactosidase enzyme activity in leukocytes or fibroblasts; however, additional testing and consideration of the patient’s clinical findings are necessary to differentiate between these conditions. Individuals with GM1 gangliosidosis can have characteristic abnormalities on urine oligosaccharides and have elevated keratan sulfate in urine (however, to a lesser degree than seen in patients with Morquio B). Individuals with Morquio B can have increased keratan sulfate in urine. Molecular sequence analysis of the GLB1 gene allows for detection of the disease-causing mutations in affected patients with GM1 gangliosidosis or Morquio B. Individuals with galactosialidosis also demonstrate abnormalities on urine oligosaccharides as well as decreased neuraminidase activity in fibroblasts. Sequencing of the CTSA gene allows for detection of disease-causing mutations in patients with galactosialidosis.

**Useful For:** Diagnosis of GM1 gangliosidosis, Morquio B disease, and galactosialidosis in whole blood specimens

**Interpretation:** Results below 5.0 nmol/hour/mL in properly submitted specimens are consistent with beta-galactosidase deficiency (GM1 gangliosidosis, Morquio B disease, or galactosialidosis). Further differentiation between GM1, Morquio B, and galactosialidosis is dependent on the patient’s clinical findings and results of additional biochemical testing. Normal results (> or =5.0 nmol/h/mL) are not consistent with beta-galactosidase deficiency.

**Reference Values:**
> or =5.0 nmol/hour/mL

An interpretive report will be provided.

Beta-Galactosidase, Blood Spot

**Clinical Information:** Beta-galactosidase is a lysosomal enzyme responsible for catalyzing the hydrolysis of gangliosides. The deficiency of this enzyme can be seen in the following conditions: GM1 gangliosidosis, Morquio syndrome B, and galactosialidosis. Enzymatic testing is not reliable for carrier detection of these conditions. GM1 gangliosidosis is an autosomal recessive lysosomal storage disorder caused by reduced or absent beta-galactosidase activity. Absent or reduced activity leads to the accumulation of GM1 gangliosides, oligosaccharides, and keratan sulfate. The disorder can be classified into 3 subtypes that vary with regard to age of onset and clinical presentation. Type 1, or infantile onset, typically presents between birth and 6 months with a very rapid progression of hypotonia, dysostosis multiplex, hepatosplenomegaly, central nervous system degeneration, and death usually by 1 to 2 years. Type 2 is generally classified as late infantile or juvenile with onset between 7 months and 3 years, presenting with developmental delays, and a having a slower progression. Type 3 is an adult or chronic variant with onset between 3 and 30 years and is typically characterized by slowly progressive dementia with Parkinsonian features and dystonia. The incidence has been estimated to be 1 in 100,000 to 200,000 live births. Mucopolysaccharidosis type IVB (MPS IVB, Morquio B) is an autosomal recessive lysosomal storage disorder caused by reduced or absent beta-galactosidase activity. The mucopolysaccharidoses are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans; GAGs). Accumulation of GAGs (also known as mucopolysaccharides) in lysosomes interferes with normal functioning of cells, tissues, and organs. MPS IVB is caused by a reduced or absent activity of the beta-galactosidase enzyme and gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms of MPS IVB are widely variable ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, hepatosplenomegaly, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. Galactosialidosis is an autosomal recessive lysosomal storage disease associated with a combined deficiency of beta-galactosidase and neuraminidase secondary to a defect in the cathepsin A protein. The disorder can be classified into 3 subtypes that vary with regard to age of onset and clinical presentation. Typical clinical presentation is coarse facial features, cherry-red spots, and skeletal dysplasia. The early infantile form is associated with fetal hydrops, skeletal dysplasia, and early death. The late infantile form typically presents with short stature dysostosis multiplex, coarse facial features, corneal clouding, hepatosplenomegaly, and heart valve problems. The juvenile/adult form is typically characterized by progressive neurologic degeneration, ataxia, and angiokeratomas. The incidence of the juvenile/adult form is greater in individuals with Japanese ancestry. Patients with mucolipidosis II/III (I-cell disease) may also demonstrate deficiency of beta-galactosidase in leukocytes, in addition to deficiency of other hydrolases. I-cell disease is an autosomal recessive lysosomal storage disorder resulting in impaired transport and phosphorylation of newly synthesized lysosomal proteins to the lysosome due to deficiency of N-acetylgalactosamine 1-phosphotransferase (GlcNAc). Characteristic clinical features include short stature, skeletal and cardiac abnormalities, and developmental delay. Measurement of beta-galactosidase activity is not the preferred diagnostic test for I-cell disease but may be included in the testing strategy. A diagnostic workup in an individual with GM1 gangliosidosis, Morquio B, or galactosialidosis typically demonstrates decreased beta-galactosidase enzyme activity in leukocytes or fibroblasts; however, additional testing and consideration of the patient’s clinical findings are necessary to differentiate between these conditions. Individuals with GM1 gangliosidosis can have characteristic abnormalities on urine oligosaccharides and have elevated keratan sulfate in urine (however to a lesser degree than seen in patients with Morquio B). Individuals with Morquio B can have increased keratan sulfate in urine. Molecular sequence analysis of the GLB1 gene allows for detection of the disease-causing mutations in affected patients with GM1 gangliosidosis or Morquio B. Individuals with galactosialidosis demonstrate abnormalities on urine oligosaccharides as well as decreased neuraminidase activity in fibroblasts. Sequencing of the CTSA gene allows for detection of

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
disease-causing mutations in patients with galactosialidosis.

**Useful For:** Diagnosis of beta-galactosidase deficiency (GM1 gangliosidosis, Morquio B disease and galactosialidosis) in blood spot specimens

**Interpretation:** Properly submitted specimens with results less than 5.0 nmol/h/mL are consistent with beta-galactosidase deficiency (GM1 gangliosidosis, Morquio B disease, or galactosialidosis). Further differentiation between GM1, Morquio B, and galactosialidosis is dependent on the patient’s clinical findings and results of additional biochemical testing. Normal results (> or =5.0 nmol/hour/mL) are not consistent with beta-galactosidase deficiency.

**Reference Values:**
> or =5.0 nmol/hour/mL
An interpretive report will be provided.

**Clinical References:**

**Beta-Galactosidase, Leukocytes**

**Clinical Information:** Beta-galactosidase is a lysosomal enzyme responsible for catalyzing the hydrolysis of gangliosides. The deficiency of this enzyme can lead to 1 of the following conditions: GM1 gangliosidosis, Morquio syndrome B, and galactosialidosis. Enzymatic testing is not reliable for carrier detection of these conditions. GM1 gangliosidosis is an autosomal recessive lysosomal storage disorder caused by reduced or absent beta-galactosidase activity. Absent or reduced activity leads to the accumulation of GM1 gangliosides, oligosaccharides, and keratan sulfate. The disorder can be classified into 3 subtypes that vary with regard to age of onset and clinical presentation. Type 1, or infantile onset, typically presents between birth and 6 months with a very rapid progression of hypotonia, dysostosis multiplex, hepatosplenomegaly, central nervous system degeneration, and death usually by 1 to 2 years. Type 2 is generally classified as late infantile or juvenile with onset between 7 months and 3 years and presenting with developmental delays or regression and a slower clinical course. Type 3 is an adult or chronic variant with onset between 3 and 30 years and is typically characterized by slowly progressive dementia with Parkinsonian features and dystonia. The incidence has been estimated to be 1 in 100,000 to 200,000 live births. Morquio B (MPS IVB) is an autosomal recessive mucopolysaccharidosis caused by reduced or absent beta-galactosidase activity resulting in the accumulation of keratan sulfate in the lysosomes. The mucopolysaccharidoses are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAG). Accumulation of GAG in lysosomes interferes with normal functioning of cells, tissues, and organs. MPS IVB typically manifests as a systemic skeletal disorder with variable severity ranging from early severe disease to a later onset attenuated form. Virtually all patients have dysostosis multiplex and short stature along with other symptoms that may include coarse facies, hepatosplenomegaly, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. Galactosialidosis is an autosomal recessive lysosomal storage disease (LSD) associated with a combined deficiency of beta-galactosidase and neuraminidase secondary to a defect in the cathepsin A protein. Clinical features are those typically associated with LSDs including coarse facial features, cherry-red spots, or skeletal dysplasia. The disorder can be classified into 3 subtypes that vary with respect to age of onset and clinical presentation. The early infantile form is associated with fetal hydrops, visceroanomaly, skeletal and ophthalmologic disorders, and early death. The late infantile form typically presents with short stature, dysostosis multiplex, coarse facial features,
hepatosplenomegaly, and/or heart valve problems. The juvenile/adult form is characterized by progressive neurologic degeneration, ataxia, cognitive disability, and/or angiokeratomas. Most of the juvenile/adult form cases have been found in individuals with Japanese ancestry. Patients with mucolipidosis II/III (I-cell disease) may also demonstrate deficiency of beta-galactosidase in leukocytes, in addition to deficiency of other hydrolases. I-cell disease is an autosomal recessive lysosomal storage disorder resulting in impaired transport and phosphorylation of newly synthesized lysosomal proteins to the lysosome due to deficiency of N-acetylgalcosamine 1-phosphotransferase (GlcNAc). Characteristic clinical features include short stature, skeletal and cardiac abnormalities, and developmental delay. Measurement of beta-galactosidase activity is not the preferred diagnostic test for I-cell disease, but may be included in the testing strategy. A diagnostic workup in an individual with GM1 gangliosidosis, Morquio B, or galactosialidosis typically demonstrates decreased beta-galactosidase enzyme activity in leukocytes and/or fibroblasts; however, additional testing and consideration of the patient's clinical findings are necessary to differentiate between these conditions. Individuals with GM1 gangliosidosis can have characteristic abnormalities on urine oligosaccharides and have elevated keratan sulfate in urine (however, to a lesser degree than seen in patients with Morquio B). Individuals with Morquio B can have increased keratan sulfate in urine. Molecular sequence analysis of the GLB1 gene allows for detection of the disease-causing mutations in affected patients with GM1 gangliosidosis and Morquio B. Individuals with galactosialidosis also demonstrate abnormalities on urine oligosaccharides as well as decreased neuraminidase activity in fibroblasts. Enzymatic testing is not reliable to detect carriers. Sequencing of the CTSA gene allows for detection of disease-causing mutations in patients with galactosialidosis.

**Useful For:** Diagnosis of GM1 gangliosidosis, Morquio B disease, and galactosialidosis

**Interpretation:** Very-low enzyme activity levels are consistent with GM1 gangliosidosis and Morquio B disease. Clinical findings must be used to differentiate between those 2 diseases. The deficiency of beta-galactosidase combined with neuraminidase deficiency (see NEURF / Neuraminidase, Fibroblasts) is characteristic of galactosialidosis.

**Reference Values:**
> or = 1.56 nmol/min/mg

**Clinical References:**

**Beta-Globin Cluster Locus Deletion/Duplication**

**Clinical Information:** Large deletions involving the beta-globin cluster locus on chromosome 11 manifest with widely variable clinical phenotypes. Up to 10% of beta-thalassemia cases (dependent on ethnicity) are caused by large deletions in the beta-globin cluster. Other thalassemias including delta-beta thalassemia, gamma-delta-beta-thalassemia, and epsilon-gamma-delta-beta-thalassemia, also result from functional loss of genes or the locus control region (LCR) that controls globin gene expression. In addition, hereditary persistence of fetal hemoglobin (HPFH) is caused by deletions of variable size along the beta-globin cluster locus. Most, but not all, of the large deletion beta-globin cluster disorders are associated with variably elevated hemoglobin (Hb) F percentages that persist after 2 years of age. In addition, most manifest in microcytosis. A notable exception is HPFH, which can have normal to minimal decreased mean corpuscular volume (MCV) values. The correct classification of these deletions is important as they confer variable predicted phenotypes and some are more protective than others when found in combination with a second beta-globin mutation, such as Hb S or beta-thalassemia. In addition,
identification of these deletions can explain lifelong microcytosis in the setting of normal iron studies and negative alpha-thalassemia molecular results.

**Useful For:**
- Determining the etiology of hereditary persistence of fetal hemoglobin (HPFH), or delta-beta-thalassemia
- Diagnosing less common causes of beta-thalassemia; these large deletional beta-thalassemia mutations result in elevated hemoglobin (Hb) A2 and usually have slightly elevated Hb F levels
- Distinguishing homozygous Hb S disease from a compound heterozygous Hb S/large beta-globin cluster deletion disorder (ie, Hb S/beta zero thalassemia, Hb S/delta beta zero thalassemia, Hb S/HPFH, Hb S/gamma-delta-beta-thalassemia) Diagnosing complex thalassemias where the beta-globin gene and 1 or more of the other genes in the beta-globin cluster have been deleted
- Evaluating and classifying unexplained increased Hb F percentages
- Evaluating microcytic neonatal anemia
- Evaluating unexplained long standing microcytosis in the setting of normal iron studies and negative alpha-thalassemia testing/normal Hb A2 percentages
- Confirming gene fusion hemoglobin variants such as Hb Lepore and Hb P-Nilotic
- Confirming homozygosity vs hemizygosity of mutations in the beta-like genes (HBB, HBD, HBG1, HBG2)

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Beta-Globin Cluster Locus Deletion/Duplication, Blood**

**Clinical Information:** Large deletions involving the beta-globin cluster locus on chromosome 11 manifest with widely variable clinical phenotypes. Up to 10% of beta-thalassemia cases (dependent on ethnicity) are caused by large deletions in the beta-globin cluster. Other thalassemias including delta-beta-thalassemia, gamma-delta-beta-thalassemia, and epsilon-gamma-delta-beta-thalassemia also result from functional loss of genes or the locus control region (LCR) that controls globin gene expression. In addition, hereditary persistence of fetal hemoglobin (HPFH) is caused by deletions of variable size along the beta globin cluster locus. Most, but not all, of the large deletion beta globin cluster disorders are associated with variably elevated hemoglobin (Hb) F percentages that persist after 2 years of age. In addition, most manifest in microcytosis. A notable exception is HPFH, which can have normal to minimal decreased mean corpuscular volume (MCV) values. The correct classification of these deletions is important as they confer variable predicted phenotypes and some are more protective than others when found in combination with a second beta globin mutation, such as Hb S or beta thalassemia. In addition, identification of these deletions can explain lifelong microcytosis in the setting of normal iron studies and negative alpha-thalassemia molecular results.

**Useful For:**
- Determining the etiology of hereditary persistence of fetal hemoglobin (HPFH), or delta-beta-thalassemia
- Diagnosing less common causes of beta-thalassemia; these large deletional beta-thalassemia mutations result in elevated hemoglobin (Hb) A2 and usually have slightly elevated Hb F levels
- Distinguishing homozygous Hb S disease from a compound heterozygous Hb S/large beta-globin cluster deletion disorder (ie, Hb S/beta zero thalassemia, Hb S/delta beta zero thalassemia, Hb S/HPFH, Hb S/gamma-delta-beta-thalassemia) Diagnosing complex thalassemias where the beta-globin gene and 1 or more of the other genes in the beta-globin cluster have been deleted
- Evaluating and classifying unexplained increased Hb F percentages
- Evaluating microcytic neonatal
Evaluating unexplained long standing microcytosis in the setting of normal iron studies and negative alpha thalassemia testing/normal Hb A2 percentages. Confirming gene fusion hemoglobin variants such as Hb Lepore and Hb P-Nilotic. Confirming homozygosity vs hemizygosity of mutations in the beta-like genes (HBB, HBD, HBG1, HBG2).

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Only orderable as a reflex. For more information see:
- HAEVP / Hemolytic Anemia Evaluation
- HBELE / Hemoglobin Electrophoresis Cascade, Blood
- MEVPE / Methemoglobinemia Evaluation
- REVE / Erythrocytosis Evaluation
- THEVP / Thalassemia and Hemoglobinopathy Evaluation

An interpretive report will be provided.

**Clinical References:**

**Beta-Globin Gene Sequencing, Blood**

**Clinical Information:** Beta-globin gene sequencing is useful in the evaluation of beta-globin chain variants and beta-thalassemia. It detects almost all beta-globin variants and the most common beta-thalassemia mutations, although prevalence is ethnicity dependent. Because these conditions are often complex, this test should always be interpreted in the context of protein studies, such as hemoglobin electrophoresis and RBC indices. The majority of beta-globin chain variants are clinically and hematologically benign; however, some have important clinical consequences, such as erythrocytosis, cyanosis/hypoxia, chronic hemolysis, or unexplained microcytosis. Most of the common clinically significant hemoglobin (Hb) variants (ie, Hb S, Hb C, Hb E, and others) are easily distinguished by hemoglobin electrophoresis and do not require molecular analysis. In addition, they are frequently found in complex hemoglobin disorders due to multiple mutations, and accurate classification requires sequencing data within the context of protein data. In some instances, beta-globin sequencing is necessary to identify or confirm the identity of rare variants, especially those associated with erythrocytosis and chronic hemolytic anemia. Rare hyperunstable variants (also termed dominant beta-thalassemia mutations) result in hemolytic anemia and do not create protein stable enough to be detectable by protein methods, including stability studies. They are not always associated with elevated Hb A2 or microcytosis and, therefore, can be electrophoretically silent. These require a high degree of clinical suspicion as all electrophoretic testing as well as stability studies cannot exclude this condition. Beta-thalassemia is an autosomal recessive condition characterized by decreased or absent synthesis of beta-globin chains due to mutations in the beta-globin gene (HBB). No abnormal protein is present and diagnosis by electrophoresis relies on hemoglobin fraction percentage alterations (ie, Hb A2 or Hb F elevations). Beta-thalassemia can be split into 3 broad classes (categorized by clinical features): 1. Beta-thalassemia trait (also called beta-thalassemia minor and beta-thalassemia carrier) (B[A]B[+] or B[A]B[0]). 2. Beta-thalassemia intermedia (B[+]B[+] or B[+]B[0]). 3. Beta-thalassemia major (B[+]B[0] or B[0]B[0]) Beta-thalassemia trait is typically a harmless condition with varying degrees of microcytosis and hypochromia and sometimes mild anemia. Transfusions are not required. Beta-thalassemia intermedia is a clinical distinction and is characterized by a more severe degree of anemia than beta-thalassemia trait with few or
intermittent transfusions required. Later in life, these individuals are at risk for iron overload even in the absence of chronic transfusion due to increased intestinal absorption of iron. Beta-thalassemia major typically comes to medical attention early in life due to severe anemia, hepatosplenomegaly, and failure to thrive. Skeletal changes are also common due to expansion of the bone marrow. Without appropriate treatment these patients have a shortened lifespan. The majority of beta-thalassemia mutations (>90%) are point mutations, small deletions, or insertions, which are detected by beta-globin gene sequencing. The remaining beta-thalassemia mutations are either due to large genomic deletions of HBB or, very rarely, trans-acting beta-thalassemia mutations located outside of the beta-globin gene cluster. Some rare beta chain variants can be clinically or electrophoretically indistinguishable from beta-thalassemia and cannot be confirmed without molecular analysis.

**Useful For:** Evaluates for the following in an algorithmic process for the HAEVP / Hemolytic Anemia Evaluation; HBELC / Hemoglobin Electrophoresis Cascade, Blood; MEVP / Methemoglobinemia Evaluation; REVE / Erythrocytosis Evaluation; THEVP / Thalassemia and Hemoglobinopathy Evaluation: -Diagnosis of beta thalassemia intermedia or major -Identification of a specific beta thalassemia mutation (ie, unusually severe beta-thalassemia trait) -Evaluation of an abnormal hemoglobin electrophoresis identifying a rare beta globin variant -Evaluation of chronic hemolytic anemia of unknown etiology -Evaluation of hereditary erythrocytosis with left-shifted p50 oxygen dissociation results -Preconception screening when there is a concern for a beta-hemoglobin disorder based on family history

**Interpretation:** The alteration will be provided with the classification, if known. Further interpretation requires correlation with protein studies and RBC indices.

**Reference Values:**

Only orderable as a reflex. For more information see:

- HAEVP / Hemolytic Anemia Evaluation
- HBELC / Hemoglobin Electrophoresis Cascade, Blood
- MEVP / Methemoglobinemia Evaluation
- REVE / Erythrocytosis Evaluation
- THEVP / Thalassemia and Hemoglobinopathy Evaluation

An interpretive report will be provided.


**Beta-Glucosidase, Leukocytes**

**Clinical Information:** Gaucher disease is an autosomal recessive lysosomal storage disorder caused by reduced or absent acid beta-glucosidase (glucocerebrosidase) enzyme activity. Absent or reduced activity of this enzyme results in accumulation of glucocerebroside in the lysosomes and interferes with the normal functioning of cells. Clinical features and severity of symptoms are widely variable within Gaucher disease, but in general, the disorder is characterized by abnormal blood parameters such as decreased red blood cells (anemia) and/or platelets (thrombocytopenia), bone disease, and hepatosplenomegaly. Individuals with more severe types of Gaucher disease may have central nervous system (CNS) involvement. There are 3 clinical subtypes of the disorder that vary with respect to age of onset and clinical presentation. Type 1 is the most common type, representing 95% of all cases, and is generally characterized by bone disease, hepatosplenomegaly, anemia and thrombocytopenia, coagulation abnormalities, lung disease, and no CNS involvement. Type 2 typically has a very severe progression with onset in the first 2 years of life including neurologic disease, hepatosplenomegaly, and lung disease, with death usually between 2 and 4 years due to lung failure. Individuals with type 3 may
have onset prior to 2 years of age, but the progression is not as severe and they may survive into the third and fourth decade. Finally, there is a perinatal lethal form associated with skin abnormalities and nonimmune hydrops fetalis, and a cardiovascular form presenting with calcification of the aortic and mitral valves, mild splenomegaly, and corneal opacities. Treatment is available in the form of enzyme replacement therapy, substrate reduction therapy, and/or chaperone therapy for types 1 and 3. Individuals with type 3 may benefit from bone marrow transplantation. Currently, only supportive therapy is available for type 2. The incidence of type 1 ranges from 1 in 20,000 to 200,000 in the general population, but is much more frequent among Ashkenazi Jews with an incidence between 1 in 400 and 900. Types 2 and 3 both have an incidence of approximately 1 in 100,000 in the general population. A diagnostic workup for Gaucher disease may demonstrate the characteristic finding of "Gaucher cells" on bone marrow examination. Significantly reduced or absent enzyme activity of acid beta-glucosidase is diagnostic. Additionally, the biomarker, glucosylsphingosine is elevated in symptomatic patients and supports a diagnosis of Gaucher disease (GPSY / Glucosylsphingosine, Blood Spot). A targeted mutation panel may allow for detection of disease-causing mutations in affected patients (GAUP / Gaucher Disease, Mutation Analysis, GBA). In addition, full sequencing of the GBA gene allows for detection of disease-causing mutations in affected patients in whom a targeted mutation panel identifies no mutations or only a single mutation (GBAZ / Gaucher Disease, Full Gene Analysis).

**Useful For:** Diagnosis of Gaucher disease

**Interpretation:** Individuals affected with Gaucher disease will have enzyme levels less than 8.7 nmol/h/mg protein. In our experience some carriers will also have less than 8.7 nmol/h/mg protein activity.

**Reference Values:**

> or =8.7 nmol/h/mg protein  

Note: Results from this assay do not reflect carrier status because of individual variation of beta-glucosidase enzyme levels. For carrier testing, order molecular test GAUP / Gaucher Disease, Mutation Analysis, GBA.

**Clinical References:**


**Beta-Human Chorionic Gonadotropin, Quantitative, Serum**

**Clinical Information:** Human chorionic gonadotropin (hCG) is a glycoprotein hormone (molecular weight: MW approximately 36,000 Dalton: Da) consisting of 2 noncovalently bound subunits. The alpha subunit (92-amino acids; "naked" protein MW 10,205 Da) is essentially identical to that of luteinizing hormone (LH), follicle-stimulating hormone, and thyroid-stimulating hormone (TSH). The alpha subunit is essential for receptor transactivation. The different beta subunits of the above hormones are transcribed from separate genes, show less homology, and convey the receptor-specificity of the dimeric hormones. The chorionic gonadotropin, beta gene (coding for a 145-amino acid, "naked" protein MW 15,531 Da, glycosylated subunit MW approximately 22,500 Da) is highly homologous to the beta subunit of LH and acts through the same receptor. However, while LH is a classical tropic pituitary hormone, hCG does not usually circulate in significant concentrations. In pregnant primates (including humans) it is synthesized in the placenta and maintains the corpus luteum and, hence, progesterone production, during the first trimester. Thereafter, the placenta produces steroid hormones, diminishing the role of hCG. hCG concentrations fall, leveling off around week 20, significantly above prepregnancy levels. After delivery, miscarriage, or pregnancy termination, hCG falls with a half-life of 24 to 36 hours, until prepregnancy levels are reached. Outside of pregnancy, hCG may be secreted by abnormal germ cell, placental, or embryonal tissues, in particular seminomatous and nonseminomatous testicular tumors; ovarian germ cell
tumors; gestational trophoblastic disease (GTD: hydatidiform mole and choriocarcinoma); and benign or malignant nontesticular teratomas. Rarely, other tumors including hepatic, neuroendocrine, breast, ovarian, pancreatic, cervical, and gastric cancers may secrete hCG, usually in relatively modest quantities. During pathological hCG production, the highly coordinated secretion of alpha and beta subunits of hCG may be disturbed. In addition to secreting intact hCG, tumors may produce disproportionate quantities of free alpha-subunits or, more commonly, free beta-subunits. Assays that detect both intact hCG and free beta-hCG, including this assay, tend to be more sensitive in detecting hCG-producing tumors. With successful treatment of hCG-producing tumors, hCG levels should fall with a half-life of 24 to 36 hours, and eventually return to the reference range.

Useful For: Monitoring patients for retained products of conception Aiding in the diagnosis of gestational trophoblastic disease (GTD), testicular tumors, ovarian germ cell tumors, teratomas, and, rarely, other human chorionic gonadotropin (hCG)-secreting tumors Serial measurement of hCG following treatment for: -Monitoring therapeutic response in GTD or in hCG-secreting tumors -Detecting persistent or recurrent GTD or hCG-secreting tumors

Interpretation: After delivery, miscarriage, or pregnancy termination, human chorionic gonadotropin (hCG) falls with a half-life of 24 to 36 hours, until prepregnancy levels are reached. An absent or significantly slower decline is seen in patients with retained products of conception. Gestational trophoblastic disease (GTD) is associated with very considerable elevations of hCG, usually above 2 multiples of the medians for gestational age persisting or even rising beyond the first trimester. Serum hCG levels are elevated in approximately 40% to 50% of patients with nonseminomatous testicular cancer and 20% to 40% of patients with seminoma. Markedly elevated levels of hCG (>5,000 IU/L) are uncommon in patients with pure seminoma and indicate the presence of a mixed testicular cancer. Ovarian germ cell tumors (approximately 10% of ovarian tumors) display elevated hCG levels in 20% to 50% of cases. Teratomas in children may overproduce hCG, even when benign, resulting in precocious pseudopuberty. Levels may be elevated to similar levels as seen in testicular cancer. Among nonreproductive tumors, hepatobiliary tumors (hepatoblastomas, hepatocellular carcinomas, and cholangiocarcinomas) and neuroendocrine tumors (e.g., islet cell tumors and carcinoids) are those most commonly associated with hCG production. Many hCG-producing tumors also produce other embryonic proteins or antigens, in particular alpha fetoprotein (AFP). AFP should, therefore, also be measured in the diagnostic workup of such neoplasms. Complete therapeutic response in hCG-secreting tumors is characterized by a decline in hCG levels with an apparent half-life of 24 to 36 hours and eventual return to concentrations within the reference range. GTD and some tumors may produce hyperglycoslated hCG with a longer half-life, but an apparent half-life of more than 3 days suggests the presence of residual hCG-producing tumor tissue. A rise in hCG levels above the reference range in patients with hCG-producing tumors that had previously been treated successfully, suggests possible local or distant metastatic recurrence.

Reference Values:
Children(1,2)

Males
Birth-3 months: < or =50 IU/L*
>3 months-<18 years: <1.4 IU/L

Females
Birth-3 months: < or =50 IU/L*
>3 months-<18 years: <1.0 IU/L

* hCG, produced in the placenta, partially passes the placental barrier. Newborn serum beta-hCG concentrations are approximately 1/400th of the corresponding maternal serum concentrations, resulting in neonate beta-hCG levels of 10-50 IU/L at birth. Clearance half-life is approximately 2-3 days. Therefore, by 3 months of age, levels comparable to adults should be reached.

Adults (97.5th percentile)
Males: <1.4 IU/L
Females
Premenopausal, nonpregnant: <1.0 IU/L
Postmenopausal: <7.0 IU/L

Newborn serum beta-hCG concentrations are approximately 1/400th of the corresponding maternal serum concentrations, resulting in neonate beta-hCG levels of 10-50 IU/L at birth. Clearance half-life is approximately 2-3 days. Therefore, by 3 months of age, levels comparable to adults should be reached.

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Pediatric reference values based on:


Beta-Human Chorionic Gonadotropin, Quantitative, Spinal Fluid

Clinical Information: Human chorionic gonadotropin (hCG) is synthesized during pregnancy by syncytiotrophoblast cells. hCG may also be produced by neoplastic cells of testicular tumors (seminomas or nonseminomas), ovarian germ cell tumors, gestational trophoblastic disease, choriocarcinoma and various nonthrophoblastic tumors including breast, ovarian, pancreatic, cervical, gastric, and hepatic cancers. Measurement of hCG is used as an adjunct in the diagnosis of germ cell tumors. The presence of hCG in cerebrospinal fluid (CSF) is suggestive of tumor presence. Pure germinomas are associated with low hCG concentrations in both serum and CSF. A subset of nongerminomatous germ cell tumors contains syncytiotrophoblastic giant cells. These tumors are associated with moderately increased hCG concentrations (<1,000 IU/L) in the serum and/or CSF, and the survival rate in patients suffering these tumors is worse than that of patients with pure germinomas. In contrast, choriocarcinomas, another subset of nongerminomatous germ cell tumors, are associated with high hCG concentrations (1,000 IU/L) in both serum and CSF. Quantification of the hCG in CSF can be important in guiding treatment and monitoring response to treatment of these tumors. The combination of the specific antibodies used in the Roche Beta hCG immunoassay recognize the holo-hormone, "nicked" forms of hCG, the beta-core fragment, and the free beta-subunit.

Useful For: As an aid in the diagnosis of brain metastases of testicular cancer or extragonadal intracerebral germ cell tumors

Interpretation: Elevated levels of human chorionic gonadotropin in spinal fluid indicate the probable presence of central nervous system metastases or recurrence of tumor in patients with germ cell tumors, including patients with testicular cancer or choriocarcinoma.

Reference Values:
<1.0 IU/L


Beta-Hydroxybutyrate, Serum

Clinical Information: Beta-hydroxybutyrate (BHB) is 1 of 3 sources of ketone bodies. Its relative proportion in the blood (78%) is greater than the other 2 ketone bodies, acetoacetate (20%) and acetone (2%). During carbohydrate deprivation (starvation, digestive disturbances, frequent vomiting), decreased
carbohydrate utilization (diabetes mellitus), glycogen storage diseases, and alkalosis, acetoacetate production increases. The increase may exceed the metabolic capacity of the peripheral tissues. As acetoacetate accumulates in the blood, a small amount is converted to acetone by spontaneous decarboxylation. The remaining and greater portion of acetoacetate is converted to BHB.

**Useful For:** Monitoring therapy for diabetic ketoacidosis Investigating the differential diagnosis of any patient presenting to the emergency room with hypoglycemia, acidosis, suspected alcohol ingestion, or an unexplained increase in the anion gap In pediatric patients, the presence or absence of ketonemia/uria is an essential component in the differential diagnosis of inborn errors of metabolism

**Interpretation:** The beta-hydroxybutyrate (BHB)/acetoacetate ratio is typically between 3:1 and 7:1 in severe ketotic states. Serum BHB increases in response to fasting, but should not exceed 0.4 mmol/L following an overnight fast (up to 12 hours). In pediatric patients, a hypo- or hyper-ketotic state (with or without hypoglycemia) may suggest specific groups of metabolic disorders.

**Reference Values:**
<0.4 mmol/L

**Clinical References:**

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**Beta-Lactamase**

**Clinical Information:** Various bacteria produce a class of enzymes called beta-lactamases, which may be mediated by genes on plasmids or chromosomes. Production of beta-lactamase may be constitutive or induced by exposure to antimicrobials. Beta-lactamases hydrolyze (and thereby inactivate) the beta-lactam rings of a variety of susceptible penicillins and cephalosporins. Beta-lactamases are classified by their preferred antimicrobial substrate and the effect of various inhibitors (such as clavulanic acid) on them. Some antimicrobials, such as cefazolin and cloxacillin are resistant to such hydrolysis (at least for staphylococcal beta-lactamases). Beta-lactamase producing strains of the following are resistant to many types of penicillin: Staphylococcus species, Hemophilus influenzae, Neisseria gonorrhoeae, Bacteroides species, Enterococcus species, and Moraxella catarrhalis. The above organisms, when isolated from critical specimens such as blood or spinal fluid, should always be tested for beta-lactamase production. Addition of a beta-lactamase inhibitor to a beta-lactam (such as sulbactam plus ampicillin) restores the activity of the antimicrobials.

**Useful For:** Predicting the resistance of beta-lactamase producing isolates to hydrolysis-susceptible beta-lactam antimicrobials

**Interpretation:** A positive test indicates production of beta-lactamase.

**Reference Values:**
Negative (reported as positive or negative)

**Clinical References:**

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**Beta-Lactoglobulin, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE
antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


IBETH 7288

Bethesda Units

Reference Values:

0 unit

HCO3 876

Bicarbonate, Serum

Clinical Information: Bicarbonate is the second largest fraction of the anions in plasma. Included in this fraction are the bicarbonate (HCO3[-]) and carbonate (CO3[-2]) ions, carbon dioxide in physical solution, as well as the carbamino compounds. At the physiological pH of blood, the concentration of carbonate is 1/1000 that of bicarbonate. The carbamino compounds are also present in such low quantities that they are generally not mentioned specifically. The bicarbonate content of serum or plasma is a significant indicator of electrolyte dispersion and anion deficit. Together with pH determination, bicarbonate measurements are used in the diagnosis and treatment of numerous potentially serious disorders associated with acid-base imbalance in the respiratory and metabolic systems. Some of these conditions are diarrhea, renal tubular acidosis, carbonic anhydrase inhibitors, hyperkalemic acidosis, renal failure, and ketoacidosis.
Useful For: Diagnosis and treatment of acid-base imbalance in respiratory and metabolic systems

Interpretation: Alterations of bicarbonate (HCO3) and carbon dioxide (CO2) dissolved in plasma are characteristic of acid-base imbalance. The nature of the imbalance cannot, however, be inferred from the bicarbonate value itself, and the determination of bicarbonate is rarely ordered alone. Its value has significance in the context of other electrolytes determined with it and in screening for electrolyte imbalance.

Reference Values:
Males
12-24 months: 17-25 mmol/L
3 years: 18-26 mmol/L
4-5 years: 19-27 mmol/L
6-7 years: 20-28 mmol/L
8-17 years: 21-29 mmol/L
> or =18 years: 22-29 mmol/L
Females
1-3 years: 18-25 mmol/L
4-5 years: 19-26 mmol/L
6-7 years: 20-27 mmol/L
8-9 years: 21-28 mmol/L
> or =10 years: 22-29 mmol/L

Reference values have not been established for patients that are <12 months of age.


FBIU

90357

Bicarbonate, Urine

Reference Values:
Reporting limit determined each analysis.

Normally: None Detected
Units: molar

BAPS

62538

Bile Acid Profile, Serum

Clinical Information: Bile acids are formed in the liver from cholesterol, conjugated primarily to glycine and taurine, stored and concentrated in the gallbladder, and secreted into the intestine after the ingestion of a meal. In the intestinal lumen, the bile acids serve to emulsify ingested fats and thereby promote digestion. During the absorptive phase of digestion, approximately 90% of the bile acids are reabsorbed. The efficiency of the hepatic clearance of bile acids from portal blood maintains serum concentrations at low levels in normal persons. An elevated fasting level, due to impaired hepatic clearance, is a sensitive indicator of liver disease. Following meals, serum bile acid levels have been shown to increase only slightly in normal persons, but markedly in patients with various liver diseases, including cirrhosis, hepatitis, cholestasis, portal-vein thrombosis, Budd-Chiari syndrome, cholangitis, Wilson disease, and hemochromatosis. No increase in bile acids will be noted in patients with intestinal malabsorption. Metabolic hepatic disorders involving organic anions (eg, Gilbert disease, Crigler-Najjar syndrome, and Dubin-Johnson syndrome) do not cause abnormal serum bile acid concentrations. The concentration of bile acids in serum is influenced by many different liver diseases due to the inability of the liver to efficiently extract circulating bile acids from portal blood. In addition, bile acid levels are altered in several biochemical genetic conditions, such as peroxisomal biogenesis disorders like Zellweger syndrome and disorders of bile acid synthesis such as D-bifunctional protein deficiency and alpha methyl-CoA racemase deficiency, due to the loss of specific enzymes important for bile acid metabolism. This analysis includes a quantitative characterization of primary and secondary bile acids.
as well as 2 bile acid precursor species for the assessment of bile acid metabolism.

**Useful For:** Evaluating the enterohepatic cycle consisting of the biliary system, intestine, portal circulation, and hepatocytes Supporting researchers in need of free and conjugated values of all 20 bile acid species as well as total bile acid

**Interpretation:** Total bile acids are metabolized in the liver and can serve as a marker for normal liver function. Increases in serum C27 bile acids are seen in patients with peroxisomal biogenesis disorders such as Zellweger syndrome or single enzyme defects of bile acid synthesis such as D-bifunctional protein deficiency and alpha methyl CoA racemases. Totals of the free and conjugated bile acid species for all 20 bile acids in addition to total bile acids will be reported. No interpretive report will be provided.

**Reference Values:**

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Normal (nmol/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chenodeoxycholic acid</td>
<td>&lt; or =2.26</td>
</tr>
<tr>
<td>Cholic acid</td>
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<tr>
<td>Deoxycholic acid</td>
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<td>Dihydroxycholestanolic acid</td>
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</tr>
<tr>
<td>Glycochenodeoxycholic acid</td>
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</tr>
<tr>
<td>Glycocholic acid</td>
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</tr>
<tr>
<td>Glycodeoxycholic acid</td>
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</tr>
<tr>
<td>Glycohinydooxycholic acid</td>
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<td>Glycolithocholic acid</td>
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</tr>
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<td>Glycoursodeoxycholic acid</td>
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<tr>
<td>Hyodeoxycholic acid</td>
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<tr>
<td>Lithocholic acid</td>
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<td>Taurochenodeoxycholic acid</td>
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<tr>
<td>Taurocholic acid</td>
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<tr>
<td>Taurodeoxycholic acid</td>
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<td>Taurohydooxycholic acid</td>
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<td>Taurolithocholic acid</td>
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</tr>
<tr>
<td>Tauroursodeoxycholic acid</td>
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<tr>
<td>Trihydroxycholestanolic acid</td>
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<tr>
<td>Ursodeoxycholic acid</td>
<td>&lt; or =0.64</td>
</tr>
<tr>
<td>Total bile acids</td>
<td>&lt; or =19.00</td>
</tr>
</tbody>
</table>

**Clinical Information:** Bile acids are formed in the liver from cholesterol, conjugated primarily to glycine and taurine, stored and concentrated in the gallbladder, and secreted into the intestine after the ingestion of a meal. In the intestinal lumen, the bile acids serve to emulsify ingested fats and thereby promote digestion. During the absorptive phase of digestion, approximately 90% of the bile acids are reabsorbed. The efficiency of the hepatic clearance of bile acids from portal blood maintains serum concentrations at low levels in normal persons. An elevated fasting level, due to impaired hepatic clearance, is a sensitive indicator of liver disease. Following meals, serum bile acid levels have been shown to increase only slightly in normal persons, but markedly in patients with various liver diseases, including cirrhosis, hepatitis, cholestasis, portal-vein thrombosis, Budd-Chiari syndrome, cholangitis, Wilson disease, and hemochromatosis. No increase in bile acids will be noted in patients with intestinal malabsorption. Metabolic hepatic disorders involving organic anions (eg, Gilbert disease, Crigler-Najjar syndrome, and Dubin-Johnson syndrome) do not cause abnormal serum bile acid concentrations. This bile acid test for peroxisomal disorders measures levels of C27 bile acids, which are diagnostic markers for peroxisomal biogenesis disorders such as Zellweger syndrome and single enzyme defects of bile acid synthesis such as D-bifunctional protein deficiency and alpha methyl-CoA racemase deficiency. Elevated levels of C27 bile acids may enable diagnosis of peroxisomal biogenesis disorders and bile acid synthesis defects in children with liver cholestasis. Treatment for peroxisomal biogenesis disorders and bile acid synthesis defects with cholic acid is available. Measurement of C27 bile acids before and during treatment with bile acid therapy such as cholic acid can assist with monitoring of treatment efficacy.

**Useful For:** Biomarker for peroxisomal biogenesis disorders such as Zellweger syndrome and single enzyme defects of bile acid synthesis including D-bifunctional protein deficiency and alpha methyl CoA racemases Monitoring patients receiving bile acid therapy such as cholic acid for liver disease due to peroxisomal biogenesis disorders or single enzyme defects in bile acid synthesis

**Interpretation:** Increases in serum C27 bile acids are seen in patients with peroxisomal biogenesis disorders such as Zellweger syndrome or single enzyme defects of bile acid synthesis such as D-bifunctional protein deficiency and alpha methyl CoA racemases. Total bile acids are metabolized in the liver and can serve as a marker for normal liver function. The values of 2 bile acid precursors, dihydroxycholestanolic acid and trihydroxycholestanolic acid, will be reported, along with total cholic acid, total chenodeoxycholic acid, total ursodeoxycholic acid, and total bile acids. No interpretive report will be provided.

**Reference Values:**
- Dihydroxycholestanolic Acid < or =0.10 nmol/mL
- Trihydroxycholestanolic Acid < or =1.30 nmol/mL
- Total Cholic Acid < or =5.00 nmol/mL
- Total Chenodeoxycholic Acid < or =6.00 nmol/mL
- Total Ursodeoxycholic Acid < or =2.00 nmol/mL
- Total Bile Acids < or =19.00 nmol/mL

**Clinical References:**

**BA48F Bile Acids, Bowel Dysfunction, 48 Hour, Feces**

**Clinical Information:** Bile acids are natural products of cholesterol synthesis that aid in the
emulsification and absorption of dietary fats in the small intestine. The majority of bile acids are reabsorbed in the ileum of the healthy individual, with only 5% excreted in feces. (1) Primary bile acids cholic acid (CA) and chenodeoxycholic acid (CDCA) are deconjugated and dehydroxylated via intestinal bacteria into secondary bile acids deoxycholic acid (DCA) and lithocholic acid (LCA), respectively. (2) The sum of CA, CDCA, DCA, LCA, and ursodeoxycholic acid (UDCA) compose the majority of bile acids in the feces. Impaired absorption of bile acids in the terminal ileum leads to excess bile acids in the colon that can cause diarrhea from chloride and water secretion; a condition called bile acid malabsorption (BAM). Irritable bowel syndrome (IBS) is a nonspecific multifactorial disorder involving the large intestine. IBS is characterized by cramping, bloating, diarrhea, and constipation and classified as either IBS-D (diarrhea) or IBS-C (constipation) by the Rome III criteria. (3) Up to 50% of IBS-D patients have accelerated colonic transit time; the mechanism of IBS-D pathophysiology is varied with more than 25% having BAM. (1, 4) Several methods have been developed for detection of BAM, but are not widely available in clinical practice. (5) Therefore, patients are often placed on trials of bile acids sequestrants to determine if symptoms improve. Quantitation of fecal bile acids aids in screening for IBS-D and identification of patients with chronic diarrhea who may benefit from bile acid sequestrant therapy.

**Useful For:**
Aids to evaluate patients suspected of having irritable bowel syndrome-diarrhea (IBS-D) symptoms due to bile acid malabsorption

**Interpretation:**
Elevated total fecal bile acid is consistent with the diagnosis of bile acid malabsorption. Pharmacological treatment with bile acid sequestrants has been shown to improve symptoms in some patients.

**Reference Values:**
Sum of cholic acid and chenodeoxycholic acid ≤3.7%
Total bile acids ≤2,619 mcmoles/48 hours

**Clinical References:**

**Bile Acids, Fractionated and Total, Serum**

**Clinical Information:**
Bile acids are formed in the liver from cholesterol, conjugated primarily to glycine and taurine, stored and concentrated in the gallbladder, and secreted into the intestine after the ingestion of a meal. In the intestinal lumen, the bile acids serve to emulsify ingested fats and thereby promote digestion. During the absorptive phase of digestion, approximately 90% of the bile acids are reabsorbed. The efficiency of the hepatic clearance of bile acids from portal blood maintains serum concentrations at low levels in normal persons. An elevated fasting level, due to impaired hepatic clearance, is a sensitive indicator of liver disease. Following meals, serum bile acid levels have been shown to increase only slightly in normal persons, but markedly in patients with various liver diseases, including cirrhosis, hepatitis, cholestasis, portal-vein thrombosis, Budd-Chiari syndrome, cholangitis, Wilson disease, and hemochromatosis. No increase in bile acids will be noted in patients with intestinal malabsorption. Metabolic hepatic disorders involving organic anions (e.g., Gilbert disease, Crigler-Najjar syndrome, and Dubin-Johnson syndrome) do not cause abnormal serum bile acid concentrations.

**Useful For:**
Measuring tauro- and glycol-conjugated and unconjugated bile acid constituents in serum
Monitoring patients receiving bile acid therapy, such as cholic acid, deoxycholic acid, or ursodeoxycholic acid
Aiding in the evaluation of liver function; evaluation of liver function changes before the formation...
of more advanced clinical signs of illness such as icterus. Determining hepatic dysfunction as a result of chemical and environmental injury. Indicating hepatic histological improvement in chronic hepatitis C patients responding to interferon treatment. Indicating intrahepatic cholestasis of pregnancy.

**Interpretation:** Total bile acids are metabolized in the liver and can serve as a marker for normal liver function. Increases in serum bile acids are seen in patients with acute hepatitis, chronic hepatitis, liver sclerosis, liver cancer, and intrahepatic cholestasis of pregnancy.

**Reference Values:**

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Normal (nmol/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholic Acid</td>
<td>&lt; or = 5.00</td>
</tr>
<tr>
<td>Total Chenodeoxycholic Acid</td>
<td>&lt; or = 6.00</td>
</tr>
<tr>
<td>Total Deoxycholic Acid</td>
<td>&lt; or = 6.00</td>
</tr>
<tr>
<td>Total Ursodeoxycholic Acid</td>
<td>&lt; or = 2.00</td>
</tr>
<tr>
<td>Total Bile Acids</td>
<td>&lt; or = 19.00</td>
</tr>
</tbody>
</table>

**Clinical References:**

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**Bile Acids, Total, Serum**

**Clinical Information:** Bile acids are formed in the liver from cholesterol, conjugated primarily to glycine and taurine, stored and concentrated in the gallbladder, and secreted into the intestine after the ingestion of a meal. In the intestinal lumen, the bile acids serve to emulsify ingested fats and thereby promote digestion. During the absorptive phase of digestion, approximately 90% of the bile acids are reabsorbed. The efficiency of the hepatic clearance of bile acids from portal blood maintains serum concentrations at low levels in normal persons. An elevated fasting level, due to impaired hepatic clearance, is a sensitive indicator of liver disease. Following meals, serum bile acid levels have been shown to increase only slightly in normal persons, but markedly in patients with various liver diseases, including cirrhosis, hepatitis, cholestasis, portal-vein thrombosis, Budd-Chiari syndrome, cholangitis, Wilson disease, and hemochromatosis. No increase in bile acids will be noted in patients with intestinal malabsorption. Metabolic hepatic disorders involving organic anions (eg, Gilbert disease, Crigler-Najjar syndrome, and Dubin-Johnson syndrome) do not cause abnormal serum bile acid concentrations. Significant increases in total bile acids in nonfasting pregnant females can aid in the diagnosis of cholestasis. Other factors, such as complete medical history, physical exam, and liver function tests should also be considered.

**Useful For:** An aid in the evaluation of liver function. Evaluation of liver function changes before the formation of more advanced clinical signs of illness such as icterus. An aid in the determination of hepatic dysfunction as a result of chemical and environmental injury. An indicator of hepatic histological improvement in chronic hepatitis C patients responding to interferon treatment. An indicator for intrahepatic cholestasis of pregnancy.

**Interpretation:** Total bile acids are metabolized in the liver and can serve as a marker for normal liver function. Increases in serum bile acids are seen in patients with acute hepatitis, chronic hepatitis, liver sclerosis, and liver cancer.

**Reference Values:**

< or = 10 mcmol/L

Reference interval applies to fasting total bile acid concentrations.

Biliary Tract Malignancy, FISH

Clinical Information: Endoscopic retrograde cholangiopancreatography (ERCP) is used to examine patients with biliary tract obstruction or stricture for possible malignancy. Biopsies and cytologic specimens are obtained at the time of ERCP. Cytologic analysis complements biopsy by sometimes detecting malignancy in patients with a negative biopsy. Nonetheless, a number of studies suggest that the overall sensitivity of bile duct brushing and bile aspirate cytology is quite low. Fluorescence in situ hybridization (FISH) is a technique that utilizes fluorescently labeled DNA probes to examine cells for chromosomal alterations. FISH can be used to detect cells with chromosomal changes (e.g., aneuploidy) that are indicative of malignancy. Studies in our laboratory indicate that the sensitivity of FISH to detect malignant cells in biliary brush specimens is superior to that of conventional cytology.

Useful For: Assessing bile duct brushing or hepatobiliary brushing specimens for malignancy

Interpretation: An interpretive report will be provided.

Reference Values: No abnormality detected by fluorescence in situ hybridization


Biliary Tract Malignancy-Cytology, FISH

Clinical Information: Endoscopic retrograde cholangiopancreatography (ERCP) is used to examine patients with biliary tract obstruction or stricture for possible malignancy. Biopsies and cytologic specimens are obtained at the time of ERCP. Cytologic analysis complements biopsy by sometimes detecting malignancy in patients with a negative biopsy. Nonetheless, a number of studies suggest that the overall sensitivity of bile duct brushing and bile aspirate cytology is quite low. Fluorescence in situ hybridization (FISH) is a technique that utilizes fluorescently labeled DNA probes to examine cells for chromosomal alterations. FISH can be used to detect cells with chromosomal changes (e.g., aneuploidy) that are indicative of malignancy. Studies in our laboratory indicate that the sensitivity of FISH to detect malignant cells in biliary brush specimens is superior to that of conventional cytology.

Useful For: Assessing bile duct brushing or hepatobiliary brushing specimens for malignancy

Interpretation: An interpretive report will be provided. A positive cytology diagnosis is normally definitive for the presence of malignancy. Suspicious or atypical results need further confirmation by clinical observation, repeat cytology, or perhaps appropriate biopsy.

Reference Values: Negative for malignancy.

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**Bilirubin Direct, Serum**

**Clinical Information:** Approximately 85% of the total bilirubin produced is derived from the heme moiety of hemoglobin while the remaining 15% is produced from the RBC precursors destroyed in the bone marrow and from the catabolism of other heme-containing proteins. After production in peripheral tissues, bilirubin is rapidly taken up by hepatocytes where it is conjugated with glucuronic acid to produce mono- and diglucuronide, which are excreted in the bile. Direct bilirubin is a measurement of conjugated bilirubin. Jaundice can occur as a result of problems at each step in the metabolic pathway. Disorders may be classified as those due to: increased bilirubin production (eg, hemolysis and ineffective erythropoiesis), decreased bilirubin excretion (eg, obstruction and hepatitis), and abnormal bilirubin metabolism (eg, hereditary and neonatal jaundice). Inherited disorders in which direct bilirubinemia occurs include Dubin-Johnson syndrome and Rotor syndrome. Jaundice of the newborn where direct bilirubin is elevated includes idiopathic neonatal hepatitis and biliary atresia. The most commonly occurring form of jaundice of the newborn, physiological jaundice, results in unconjugated (indirect) hyperbilirubinemia. Elevated unconjugated bilirubin in the neonatal period may result in brain damage (kernicterus). Treatment options are phototherapy and, if severe, exchange transfusion. The increased production of bilirubin that accompanies the premature breakdown of erythrocytes and ineffective erythropoiesis results in hyperbilirubinemia in the absence of any liver abnormality. In hepatobiliary diseases of various causes, bilirubin uptake, storage, and excretion are impaired to varying degrees. Thus, both conjugated and unconjugated bilirubin is retained and a wide range of abnormal serum concentrations of each form of bilirubin may be observed. Both conjugated and unconjugated bilirubin are increased in hepatocellular diseases such as hepatitis and space-occupying lesions of the liver, and obstructive lesions such as carcinoma of the head of the pancreas, common bile duct, or ampulla of Vater.

**Useful For:** Evaluation of jaundice and liver functions

**Interpretation:** Direct bilirubin levels must be assessed in conjunction with total and indirect levels and the clinical setting.

**Reference Values:**

- > or =12 months: 0.0-0.3 mg/dL
  - Reference values have not been established for patients who are <12 months of age.


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**Bilirubin, Amniotic Fluid**

**Clinical Information:** The presence of bilirubin in amniotic fluid, which results in a yellow color, is an indicator of fetal erythroblastosis. Visual inspection of amniotic fluid is unreliable because bilirubin is not the only cause of an excessive yellow color; therefore, the presence of bilirubin must be confirmed with spectrophotometric methods. Meconium may contribute a green color (biliverdin) that can obscure the color of bilirubin and hemoglobin.

**Useful For:** Evaluation of Rh disease, ie, hemolytic disease of the fetus Monitoring disease progression to assess need for fetal transfusion

**Interpretation:** The reference range for bilirubin in amniotic fluid is related to the gestational age of the fetus. Refer to either the Queenan Curve (gestational age <27 weeks) or the Liley Chart (gestational...
age >27 weeks) listed under Interpretation of Amniotic Fluid Bilirubin Results (Delta OD 450) in Special Instructions.

**Reference Values:**
Interpretation of fetal risk is dependent upon gestational age.
Refer to either the Queenan Curve (gestational age <27 weeks) or the Liley Chart (gestational age >27 weeks) listed under Interpretation of Amniotic Fluid Bilirubin Results (Delta OD 450) in Special Instructions.

**Clinical References:**

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**Bilirubin, Body Fluid**

**Clinical Information:** Assessing whether a body fluid specimen is exudative or transudative in nature is the initial step in determining the etiology of the fluid. Transudative fluids result from hemodynamic aberrations or oncotic changes and are associated with ultrafiltration of serum across pleural membranes. Transudates most commonly occur in association with clinically apparent conditions such as heart failure and cirrhosis. Exudative fluids tend to develop as a consequence of inflammation or malignant disorders such as tuberculosis, pneumonia, or cancer, in which capillary permeability is increased, allowing large-molecular-weight compounds to be released into the accumulating fluid. If the fluid is transudate, further diagnostic procedures are often not necessary; however the presence of an exudative fluid often triggers additional testing that may be invasive in nature. Determination of body fluid bilirubin concentration can aid in the distinction between a transudative and an exudative fluid. Bilirubin values tend to be higher in exudates than in transudates, although there is some overlap between groups. However, a ratio of body fluids to serum bilirubin has been reported to identify exudative body fluids with sensitivity, specifically, positive predictive accuracy, and absolute accuracy equivalent to that obtained using Light's criteria for an exudative pleural fluid (pleural/serum protein ratio >0.5, pleural/serum lactate dehydrogenase ratio >0.6, and serum lactate dehydrogenase >200 U/L).

**Useful For:** May aid in the distinction between a transudative and an exudative body fluid, when used in conjunction with other testing including serum bilirubin analysis, body fluid: serum protein ratio, body fluids: serum lactate dehydrogenase ratio, and serum lactate dehydrogenase

**Interpretation:** Elevated body fluid bilirubin is suggestive of an exudative fluid. This testing should be performed in conjunction with other testing including serum bilirubin analysis, body fluid: serum protein ratio, body fluids : serum lactate dehydrogenase ratio, and serum lactate dehydrogenase.

**Reference Values:**
Not applicable
The reference range has not been established for bilirubin in body fluids. The test result should be integrated into the clinical context for interpretation.

**Clinical References:**

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**Bilirubin, Serum**

**Clinical Information:** Assessing whether a body fluid specimen is exudative or transudative in nature is the initial step in determining the etiology of the fluid. Transudative fluids result from hemodynamic aberrations or oncotic changes and are associated with ultrafiltration of serum across pleural membranes. Transudates most commonly occur in association with clinically apparent conditions such as heart failure and cirrhosis. Exudative fluids tend to develop as a consequence of inflammation or malignant disorders such as tuberculosis, pneumonia, or cancer, in which capillary permeability is increased, allowing large-molecular-weight compounds to be released into the accumulating fluid. If the fluid is transudate, further diagnostic procedures are often not necessary; however the presence of an exudative fluid often triggers additional testing that may be invasive in nature. Determination of body fluid bilirubin concentration can aid in the distinction between a transudative and an exudative fluid. Bilirubin values tend to be higher in exudates than in transudates, although there is some overlap between groups. However, a ratio of body fluids to serum bilirubin has been reported to identify exudative body fluids with sensitivity, specifically, positive predictive accuracy, and absolute accuracy equivalent to that obtained using Light's criteria for an exudative pleural fluid (pleural/serum protein ratio >0.5, pleural/serum lactate dehydrogenase ratio >0.6, and serum lactate dehydrogenase >200 U/L).

**Useful For:** May aid in the distinction between a transudative and an exudative body fluid, when used in conjunction with other testing including serum bilirubin analysis, body fluid: serum protein ratio, body fluids: serum lactate dehydrogenase ratio, and serum lactate dehydrogenase

**Interpretation:** Elevated body fluid bilirubin is suggestive of an exudative fluid. This testing should be performed in conjunction with other testing including serum bilirubin analysis, body fluid: serum protein ratio, body fluids: serum lactate dehydrogenase ratio, and serum lactate dehydrogenase.

**Reference Values:**
Not applicable
The reference range has not been established for bilirubin in body fluids. The test result should be integrated into the clinical context for interpretation.

**Clinical References:**
Clinical Information: Bilirubin is one of the most commonly used tests to assess liver function. Approximately 85% of the total bilirubin produced is derived from the heme moiety of hemoglobin, while the remaining 15% is produced from RBC precursors destroyed in the bone marrow and from the catabolism of other heme-containing proteins. After production in peripheral tissues, bilirubin is rapidly taken up by hepatocytes where it is conjugated with glucuronic acid to produce bilirubin mono- and diglucuronide, which are then excreted in the bile. A number of inherited and acquired diseases affect 1 or more of the steps involved in the production, uptake, storage, metabolism, and excretion of bilirubin. Bilirubinemia is frequently a direct result of these disturbances. The most commonly occurring form of unconjugated hyperbilirubinemia is that seen in newborns and referred to as physiological jaundice. The increased production of bilirubin, that accompanies the premature breakdown of erythrocytes and ineffective erythropoiesis, results in hyperbilirubinemia in the absence of any liver abnormality. The rare genetic disorders, Crigler-Najjar syndromes type I and type II, are caused by a low or absent activity of bilirubin UDP-glucuronyl-transferase. In type I, the enzyme activity is totally absent, the excretion rate of bilirubin is greatly reduced and the serum concentration of unconjugated bilirubin is greatly increased. Patients with this disease may die in infancy owing to the development of kernicterus. In hepatobiliary diseases of various causes, bilirubin uptake, storage, and excretion are impaired to varying degrees. Thus, both conjugated and unconjugated bilirubin are retained and a wide range of abnormal serum concentrations of each form of bilirubin may be observed. Both conjugated and unconjugated bilirubins are increased in hepatitis and space-occupying lesions of the liver; and obstructive lesions such as carcinoma of the head of the pancreas, common bile duct, or ampulla of Vater.

Useful For: Assessing liver function Evaluating a wide range of diseases affecting the production, uptake, storage, metabolism, or excretion of bilirubin Monitoring the efficacy of neonatal phototherapy

Interpretation: The level of bilirubinemia that results in kernicterus in a given infant is unknown. In preterm infants, the risk of a handicap increases by 30% for each 2.9 mg/dL increase of maximal total bilirubin concentration. While central nervous system damage is rare when total serum bilirubin (TSB) is less than 20 mg/dL, premature infants may be affected at lower levels. The decision to institute therapy is based on a number of factors including TSB, age, clinical history, physical examination, and coexisting conditions. Phototherapy typically is discontinued when TSB level reaches 14 to 15 mg/dL. Physiologic jaundice should resolve in 5 to 10 days in full-term infants and by 14 days in preterm infants. When any portion of the biliary tree becomes blocked, bilirubin levels will increase.

Reference Values:
Direct Bilirubin
> or =12 months: 0.0-0.3 mg/dL
Reference values have not been established for patients who are <12 months of age.

Total Bilirubin
0-6 days: Refer to www.bilitool.org for information on age-specific (postnatal hour of life) serum bilirubin values.
7-14 days: <15.0 mg/dL
15 days to 17 years: < or =1.0 mg/dL
> or =18 years: < or =1.2 mg/ dL

while the remaining 15% is produced from the red blood cell precursors destroyed in the bone marrow and from the catabolism of other heme-containing proteins. After production in peripheral tissues, bilirubin is rapidly taken up by hepatocytes where it is conjugated with glucuronic acid to produce mono- and diglucuronide, which are excreted in the bile. A number of inherited and acquired diseases affect 1 or more of the steps involved in the production, uptake, storage, metabolism, and excretion of bilirubin. Bilirubinemia is a frequent and direct result of these disturbances. Jaundice can occur as a result of problems at each step in the metabolic pathway. Disorders may be classified as those due to: increased bilirubin production (eg, hemolysis and ineffective erythropoiesis), decreased bilirubin excretion (eg, obstruction and hepatitis), and abnormal bilirubin metabolism (eg, hereditary and neonatal jaundice). The most commonly occurring form of unconjugated hyperbilirubinemia is that seen in newborns and referred to as physiological jaundice. Elevated unconjugated bilirubin in the neonatal period may result in brain damage (kernicterus). Treatment options are phototherapy and, if severe, exchange transfusion. The rare genetic disorders, Crigler-Najjar syndromes type I and type II, are caused by a low or absent activity of bilirubin UDP-glucuronyl-transferase. In type I, the enzyme activity is totally absent, the excretion rate of bilirubin is greatly reduced and the serum concentration of unconjugated bilirubin is greatly increased. Patients with this disease may die in infancy owing to the development of kernicterus. The increased production of bilirubin, that accompanies the premature breakdown of erythrocytes and ineffective erythropoiesis, results in hyperbilirubinemia in the absence of any liver abnormality. In hepatobiliary diseases of various causes, bilirubin uptake, storage, and excretion are impaired to varying degrees. Thus, both conjugated and unconjugated bilirubin is retained and a wide range of abnormal serum concentrations of each form of bilirubin may be observed. Both conjugated and unconjugated bilirubin are increased in hepatitis and space-occupying lesions of the liver; and obstructive lesions such as carcinoma of the head of the pancreas, common bile duct, or ampulla of Vater.

**Useful For:** Assessing liver function Evaluating a wide range of diseases affecting the production, uptake, storage, metabolism, or excretion of bilirubin Monitoring the efficacy of neonatal phototherapy

**Interpretation:** The level of bilirubinemia that results in kernicterus in a given infant is unknown. While central nervous system damage is rare when total serum bilirubin (TSB) is less than 20 mg/dL, premature infants may be affected at lower levels. The decision to institute therapy is based on a number of factors including TSB, age, clinical history, physical examination and coexisting conditions. Phototherapy typically is discontinued when TSB level reaches 14 to 15 mg/dL. Physiologic jaundice should resolve in 5 to 10 days in full-term infants and by 14 days in preterm infants. In preterm infants, the risk of a handicap increases by 30% for each 2.9 mg/dL increase of maximal total bilirubin concentration. When any portion of the biliary tree becomes blocked, bilirubin levels will increase.

**Reference Values:**
0-6 days: Refer to www.bilitool.org for information on age-specific (postnatal hour of life) serum bilirubin values.
7-14 days: <15.0 mg/dL
15 days to 17 years: < or =1.0 mg/dL
> or =18 years: < or =1.2 mg/dL

**Clinical References:**

**Bilirubin, Urine**

**Clinical Information:** Bilirubin is primarily derived from metabolism of hemoglobin. Only conjugated bilirubin is excreted into the urine and normally only trace amounts can be detected in urine. Elevated urinary bilirubin occurs in patients with obstructive jaundice or jaundice due to hepatocellular disease or injury. However, urine bilirubin is relatively insensitive for detection of liver disease. Hyperbilirubinemia due to hemolysis is principally due to unconjugated bilirubin, and therefore does not
result in increased urinary bilirubin.

**Useful For:** Limited use in screening of patients for liver disease.

**Interpretation:** Elevated urinary bilirubin is suggestive of hepatocellular disease or post-hepatic biliary obstruction.

**Reference Values:**
Negative
If positive, results reported as trace or positive.


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**Biotinidase Deficiency, BTD Full Gene Analysis**

**Clinical Information:** Biotinidase deficiency is an inherited metabolic disease caused by reduced levels of biotinidase, an enzyme that recycles biotin by releasing it from its metabolic product, biocytin, or exogenous dietary proteins. Biotin is a vitamin that serves as a coenzyme for 4 carboxylases that are essential for amino acid catabolism, gluconeogenesis, and fatty acid synthesis. Depletion of free biotin reduces carboxylase activity, resulting in secondary carboxylase deficiency. Depending on the amount of residual biotinidase activity, individuals can have either profound or partial biotinidase deficiency. Age of onset and clinical phenotype vary among individuals. Profound biotinidase deficiency occurs in approximately 1 in 137,000 live births and partial biotinidase deficiency occurs in approximately 1 in 110,000 live births, resulting in a combined incidence of about 1 in 61,000. Untreated profound biotinidase deficiency (<10% of normal biotinidase activity) manifests within the first decade of life as seizures, hypotonia, neurosensory hearing loss, respiratory problems, and cutaneous symptoms including skin rash, alopecia, and recurrent viral or fungal infections. Among children and adolescents with profound biotinidase deficiency, clinical features include ataxia, sensorineural hearing loss, developmental delay, and eye problems such as optic neuropathy leading to blindness. Partial biotinidase deficiency (10%-30% of normal biotinidase activity) is associated with a milder clinical presentation, which may include cutaneous symptoms without neurologic involvement. Treatment with biotin has been successful in both preventing and reversing the clinical features associated with biotinidase deficiency. As a result, biotinidase deficiency is included in most newborn screening programs in order to prevent disease. Biotinidase deficiency exhibits a similar clinical presentation to carboxylase and holocarboxylase synthetase deficiency. Therefore, measurement of the biotinidase enzyme is required to differentiate between these diseases and ensure proper diagnosis. Newborn screening for biotinidase deficiency involves direct analysis of the biotinidase enzyme from blood spots obtained shortly after birth. This enables early identification of potentially affected individuals and quick follow-up with confirmatory biochemical and molecular testing. Biotinidase deficiency is inherited in an autosomal recessive manner, caused by mutations in the biotinidase gene (BTD). The carrier frequency for biotinidase deficiency in the general population is about 1:120. Several common mutations in the BTD gene have been identified, accounting for about 60% of affected individuals. Sequencing of the entire BTD gene detects other, less common, disease-causing mutations. While genotype-phenotype correlations are not well established, it appears that certain mutations are associated with profound biotinidase deficiency, while others are associated with partial deficiency. The recommended first-tier test to screen for biotinidase deficiency is a biochemical test that measures biotinidase enzyme activity, either newborn screening or BIOTS / Biotinidase, Serum. Molecular tests form the basis of confirmatory or carrier testing. Individuals with decreased enzyme activity are more likely to have 2 identifiable mutations in the BTD gene by molecular genetic testing.

**Useful For:** Second-tier test for confirming biotinidase deficiency (indicated by biochemical testing or newborn screening) Carrier testing of individuals with a family history of biotinidase deficiency, but disease-causing mutations have not been identified in an affected individual

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.
Reference Values:
An interpretive report will be provided.


BIOTS 88205

Biotinidase, Serum

Clinical Information: Biotinidase deficiency is an autosomal recessive disorder caused by mutations in the biotinidase gene (BTD). Age of onset and clinical phenotype vary among individuals depending on the amount of residual biotinidase activity. Profound biotinidase deficiency occurs in approximately 1 in 137,000 live births and partial biotinidase deficiency occurs in approximately 1 in 110,000 live births, resulting in a combined incidence of about 1 in 61,000. The carrier frequency for biotinidase deficiency within the general population is about 1 in 120. Untreated profound biotinidase deficiency typically manifests within the first decade of life as seizures, ataxia, developmental delay, hypotonia, sensorineural hearing loss, vision problems, skin rash, and alopecia. Partial biotinidase deficiency is associated with a milder clinical presentation, which may include cutaneous symptoms without neurologic involvement. Certain organic acidurias, such as holocarboxylase synthase deficiency, isolated carboxylase synthase deficiency, and 3-methylcrotonylglycinuria, present similarly to biotinidase deficiency. Serum biotinidase levels can help rule out these disorders. Treatment with biotin is successful in preventing the clinical features associated with biotinidase deficiency. In symptomatic patients, treatment will reverse many of the clinical features except developmental delay, vision, and hearing complications. As a result, biotinidase deficiency is included in most newborn screening programs. This enables early identification and treatment of presymptomatic patients. Molecular tests form the basis of confirmatory or carrier testing. When biotinidase enzyme activity is deficient, sequencing of the entire BTD gene (BTDZ / Biotinidase Deficiency, BTD Full Gene Analysis) allows for detection of disease-causing mutations in affected patients. Identification of familial mutations allows for testing of at-risk family members (FMTT / Familial Mutation, Targeted Testing). While genotype-phenotype correlations are not well established, it appears that certain mutations are associated with profound biotinidase deficiency, while others are associated with partial deficiency.

Useful For: Preferred test for diagnosing biotinidase deficiency Follow-up testing for certain organic acidurias

Interpretation: The reference range is 3.5 U/L to 13.8 U/L. Partial deficiencies and carriers may occur at the low end of the reference range. Values below 3.5 U/L are occasionally seen in specimens from unaffected patients.

Reference Values: 3.5-13.8 U/L

### Bird Fancier's Precipitin Panel I

**Reference Values:**

<table>
<thead>
<tr>
<th>Bird Type</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canary Droppings</td>
<td>Negative</td>
</tr>
<tr>
<td>Chicken Serum</td>
<td>Negative</td>
</tr>
<tr>
<td>Cockatiel Droppings</td>
<td>Negative</td>
</tr>
<tr>
<td>Finch Droppings</td>
<td>Negative</td>
</tr>
<tr>
<td>Parakeet Droppings</td>
<td>Negative</td>
</tr>
<tr>
<td>Parakeet Serum</td>
<td>Negative</td>
</tr>
<tr>
<td>Parrot Droppings</td>
<td>Negative</td>
</tr>
<tr>
<td>Parrot Serum</td>
<td>Negative</td>
</tr>
<tr>
<td>Pigeon/Dove Droppings</td>
<td>Negative</td>
</tr>
<tr>
<td>Pigeon/Dove Serum</td>
<td>Negative</td>
</tr>
</tbody>
</table>

The gel diffusion method was used to test this patient's serum for the presence of precipitating antibodies (IgG) to the antigens indicated. These antibodies are serological markers for exposure and immunological sensitization. The clinical significance varies, depending on the history and symptoms.

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### Birt-Hogg-Dube Syndrome, Full Gene Analysis

**Clinical Information:** The clinical characteristics of Birt-Hogg-Dube syndrome (BHDS) include cutaneous manifestations (fibrofolliculomas, trichodiscomas/angiofibromas, perifollicular fibromas, and acrochordons), pulmonary cysts/history of pneumothorax, and various types of renal tumors. Skin lesions typically appear during the third and fourth decades of life and typically increase in size and number with age. Lung cysts are mostly bilateral and multifocal; most individuals are asymptomatic but have a high risk for spontaneous pneumothorax. Individuals with BHDS have an increased risk of renal tumors that are typically bilateral and multifocal and usually slow growing; median age of tumor diagnosis is 48 years with a range from 31 to 71 years. Some families have renal tumor and/or autosomal dominant spontaneous pneumothorax without cutaneous manifestations. BHDS is inherited in an autosomal dominant manner and penetrance is considered to be very high. FLCN (also known as folliculin or BHD) is the only gene known to be associated with BHDS. Sequence analysis detects mutations in FLCN in 88% of affected individuals. Recent studies have reported that multi-exonic deletions can account for up to 5% to 10% of additional mutations.(2, 3) Molecular genetic testing is indicated in all individuals known to have or suspected of having BHDS, including individuals with one of the following: -Five or more facial or truncal papules with at least 1 histologically confirmed fibrofolliculoma, with or without a family history of BHDS -Facial papules histologically confirmed to be angiofibroma in an individual who does not fit the clinical criteria of tuberous sclerosis complex (TSC) or multiple endocrine neoplasia type 1 (MEN1) -Multiple and bilateral chromophobe, oncocytic, and/or hybrid renal tumors -A single oncocytic, chromophobe, or oncocytic hybrid renal tumor and a family history of renal cancer with any of these renal cell tumor types -A family history of autosomal dominant primary spontaneous pneumothorax without a history of smoking or chronic obstructive pulmonary disease (COPD) In the absence of an increased risk of developing childhood malignancy, the American Society of Clinical Oncology (ASCO) recommends delaying genetic testing in at-risk individuals until they reach age 18 years and are able to make informed decisions regarding genetic testing.

**Useful For:** Genetic diagnosis of Birt-Hogg-Dube syndrome for clinical management, risk assessment for related clinical symptoms, and genetic counseling for family members

**Interpretation:** All detected alterations will be evaluated according to American College of Medical...
Genetics and Genomics (ACMG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

Bismuth, Blood

Clinical Information: Bismuth is used in the production of alloys, pigments, and chemical additives. Various compounds have also been used as therapeutic agents, astringents, antacids. Bismuth subsalicylate (Pepto-Bismol) is one example commonly used for indigestion and diarrhea. In unexposed individuals, bismuth blood concentrations were typically <0.02 mcg/L compared to peptic ulcer patients taking bismuth medications where the concentrations ranged from 4 to 30 mcg/L. Elimination from the body takes place primarily by the urinary and fecal routes, but the exact proportion contributed by each route is still unknown. Elimination from blood displays multicompartment pharmacokinetics with half-lives of 8 to 16 hours (early) and 5 to 11 days (late). A number of toxic effects have been attributed to bismuth compounds in humans including: nephropathy, encephalopathy, osteoarthropathy, gingivitis, stomatitis, and colitis. Common early symptoms include salivation, mucosal swelling, discoloration of the tongue, gums, abdominal pain, and nausea.

Useful For: Determining bismuth toxicity

Interpretation: Normal blood concentrations for unexposed individuals are <1 ng/mL and the therapeutic range is 4 to 30 ng/mL.

Reference Values:
<1 ng/mL (unexposed)
4-30 ng/mL (therapeutic)

Clinical References:

Bismuth, Serum

Reference Values:
Reference Range: <4.0 ng/mL

Whole blood is the preferred specimen for assessment of Bismuth exposure.
Whole blood is the preferred specimen for assessment of Bismuth exposure.

Polyomaviruses are small (45 nm, approximately 5,000 base pairs), DNA-containing viruses and include 3 closely related viruses of clinical significance, Simian virus 40 (SV-40), JC virus (JCV), and BK virus (BKV). SV-40 naturally infects rhesus monkeys but can infect humans, while BKV and JCV cause productive infection only in humans. Acquisition of BKV begins in infancy. Serological evidence of infection by BKV is present in 37% of individuals by 5 years of age and over 80% of adolescents. BKV is an important cause of interstitial nephritis and associated nephropathy (BKVAN) in recipients of kidney transplants. Up to 5% of renal allograft recipients can be affected, and among those patients the average time from transplant to diagnosis is about 40 weeks (range 6-150). PCR analysis of BKV DNA in the plasma is the most widely used blood test for the laboratory diagnosis of BKV-associated nephropathy. Importantly, the presence of BKV DNA in blood reflects the dynamics of the disease: the conversion of plasma from negative to positive for BKV DNA after transplantation, the presence of DNA in plasma in conjunction with the persistence of nephropathy, and its disappearance from plasma after the reduction of immunosuppressive therapy. Viral loads of above 10,000 copies/mL in plasma may indicate a risk for BKVAN (see QBK / BK Virus, Molecular Detection, Quantitative, PCR, Plasma).

Useful For: Rapid detection of BK virus DNA

Interpretation: Results of plasma tests are reported in terms of the presence or absence of BK virus (BKV). Detection of BKV DNA in clinical specimens may support the clinical diagnosis of renal or urologic disease due to BKV. Correlation of qualitative results with clinical presentation and BK viral load in urine and/or plasma is recommended.

Reference Values: Negative

Clinical References:
Serological evidence of infection by BKV is present in 37% of individuals by age 5 and over 80% of adolescents. BKV is an important cause of interstitial nephritis and associated nephropathy (BKVAN) in recipients of kidney transplants. Up to 5% of renal allograft recipients can be affected, and among those patients the average time from transplant to diagnosis is about 40 weeks (range 6-150). (3) PCR analysis of BKV DNA in the plasma is the most widely used blood test for the laboratory diagnosis of BKV-associated nephropathy. Importantly, the presence of BKV DNA in blood reflects the dynamics of the disease: the conversion of plasma from negative to positive for BKV DNA after transplantation, the presence of DNA in plasma in conjunction with the persistence of nephropathy, and its disappearance from plasma after the reduction of immunosuppressive therapy. (4-8) However, BKV DNA is typically detectable in urine prior to plasma and may serve as an indication of impending BKVAN. Viral loads of above 100,000 copies/mL in urine may also indicate a risk for BKVAN (see QBKU / BK Virus, Molecular Detection, Quantitative, PCR, Urine).

Useful For: Rapid detection of BK virus DNA

Interpretation: Results of urine tests are reported in terms of the presence or absence of BK virus (BKV). Detection of BKV DNA in clinical specimens may support the clinical diagnosis of renal or urologic disease due to BKV. Correlation of qualitative results with clinical presentation and BK-viral load in urine and/or plasma is recommended.

Reference Values:
Negative

Clinical References:

QBK
83187

BK Virus, Molecular Detection, Quantitative, PCR, Plasma

Clinical Information: Polyomaviruses are small (45 nm, approximately 5,000 bp), DNA-containing viruses and include 3 closely related viruses of clinical significance: Simian virus 40 (SV-40), JC virus (JCV), and BK virus (BKV). SV-40 naturally infects rhesus monkeys but can infect humans, while BKV and JCV cause productive infection only in humans. (1,2) Acquisition of BKV begins in infancy. Serological evidence of infection by BKV is present in 37% of individuals by 5 years of age and over 80% of adolescents. BKV is an important cause of interstitial nephritis and BKV-associated nephropathy (BKVAN) in recipients of kidney transplants. Up to 5% of renal allograft recipients can be affected, and among those patients the average time from transplant to diagnosis is about 40 weeks (range 6-150). (3) Quantitative PCR analysis of BKV DNA in the plasma is the most widely used blood test for the laboratory diagnosis of BKV-associated nephropathy. Importantly, the presence of BKV DNA in blood reflects the dynamics of the disease: the conversion of plasma from negative to positive for BKV DNA after transplantation, the presence of DNA in plasma in conjunction with the persistence of nephropathy, and its disappearance from plasma after the reduction of immunosuppressive therapy. (4-8) The presence of BKV DNA in plasma at levels at or above 10,000 copies BKV DNA/mL may correlate with an increased risk of BKVAN with this assay. Furthermore, the trend of viral DNA quantitation (eg, increasing, decreasing) may be helpful in predicting the onset of BKVAN.

Useful For: A prospective and diagnostic marker for the development of nephropathy in renal transplant recipients
Interpretation: Increasing copy levels of BK virus (BKV) DNA in serial specimens may indicate possible BKV-associated nephropathy (BKVAN) in kidney transplant patients. Viral loads above 10,000 copies/mL in plasma may also indicate a risk for BKVAN. This assay does not cross react with other polyomaviruses, including JC virus and Simian virus 40 (SV-40).

Reference Values:
None detected

Clinical References:

BK Virus, Molecular Detection, Quantitative, PCR, Urine

Clinical Information: Polyomaviruses are small (45 nm, approximately 5,000 bp), DNA-containing viruses and include 3 closely related viruses of clinical significance; SV-40, JC virus (JCV) and BK virus (BKV). SV-40 naturally infects rhesus monkeys but can infect humans, while BKV and JCV cause productive infection only in humans.(1-2) Acquisition of BKV begins in infancy. Serological evidence of infection by BKV is present in 37% of individuals by 5 years of age and over 80% of adolescents. BKV is an important cause of interstitial nephritis and associated nephropathy (BKVAN) in recipients of kidney transplants. Up to 5% of renal allograft recipients can be affected, and among those patients the average time from transplant to diagnosis is about 40 weeks (range 6-150).(3) PCR analysis of BKV DNA in the plasma is the most widely used blood test for the laboratory diagnosis of BKV-associated nephropathy. Importantly, the presence of BKV DNA in blood reflects the dynamics of the disease: the conversion of plasma from negative to positive for BKV DNA after transplantation, the presence of DNA in plasma in conjunction with the persistence of nephropathy, and its disappearance from plasma after the reduction of immunosuppressive therapy.(4-8) However, BKV DNA is typically detectable in urine prior to plasma and may serve as an indication of impending BKVAN. Viral loads of greater than 100,000 copies/mL in urine may also indicate a risk for BKVAN.

Useful For: A prospective and diagnostic marker for the development of BK virus nephropathy in renal transplant recipients

Interpretation: Increasing copy levels of BK virus (BKV) DNA in serial specimens may indicate possible BKV-associated nephropathy (BKVAN) in kidney transplant patients. Viral loads of above 100,000 copies/mL in urine may also indicate a risk for BKVAN. This assay does not cross react with other polyomaviruses, including JC virus and SV-40.

Reference Values:
None detected

Clinical References:
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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**BLAST 35793**

**Blastomyces Antibody by EIA, Serum**

**Clinical Information:** The dimorphic fungus, Blastomyces dermatitidis, causes blastomycosis. When the organism is inhaled, it causes pulmonary disease-cough, pain, and hemoptysis, along with fever and night sweats. It commonly spreads to the skin, bone, or internal genitalia where suppuration and granulomas are typical. Occasionally, primary cutaneous lesions after trauma are encountered; however, this type of infection is uncommon.

**Useful For:** Detection of antibodies in patients having blastomycosis

**Interpretation:** A positive result indicates that IgG and/or IgM antibodies to Blastomyces were detected. The presence of antibodies is presumptive evidence that the patient was or is currently infected with (or was exposed to) Blastomyces. A negative result indicates that antibodies to Blastomyces were not detected. The absence of antibodies is presumptive evidence that the patient was not infected with Blastomyces. However, the specimen may have been obtained before antibodies were detectable or the patient may be immunosuppressed. If infection is suspected, another specimen should be drawn 7 to 14 days later and submitted for testing. Specimens testing equivocal will be submitted for further testing by another conventional serologic test (eg, SBL / Blastomyces Antibody by Immunodiffusion, Serum).
Blastomyces Antibody by Immunodiffusion, Serum

**Clinical Information:** The dimorphic fungus, Blastomyces dermatitidis, causes blastomycosis. When the organism is inhaled, it causes pulmonary disease—cough, pain, and hemoptysis, along with fever and night sweats. It commonly spreads to the skin, bone, or internal genitalia where suppuration and granulomas are typical. Occasionally, primary cutaneous lesions after trauma are encountered; however, this type of infection is uncommon.

**Useful For:** Detection of antibodies in serum specimens in patients with blastomycosis

**Interpretation:** A positive result is suggestive of infection, but the results cannot distinguish between active disease and prior exposure. Routine culture of clinical specimens (eg, respiratory specimen) is recommended in cases of suspected active blastomycosis.

**Reference Values:** Negative


Blastomyces Antibody by Immunodiffusion, Spinal Fluid

**Clinical Information:** The dimorphic fungus, Blastomyces dermatitidis, causes blastomycosis. When the organism is inhaled, it causes pulmonary disease—cough, pain, and hemoptysis, along with fever and night sweats. It commonly spreads to the skin, bone, or internal genitalia where suppuration and granulomas are typical. Occasionally, primary cutaneous lesions after trauma are encountered; however, this type of infection is uncommon. Central nervous system disease is uncommon.

**Useful For:** Detection of antibodies in spinal fluid specimens from patients with blastomycosis

**Interpretation:** A positive result is suggestive of infection, but the results cannot distinguish between active disease and prior exposure. Furthermore, detection of antibodies in cerebrospinal fluid (CSF) may reflect intrathecal antibody production, or may occur due to passive transfer or introduction of antibodies from the blood during lumbar puncture. Routine fungal culture of clinical specimens (eg, CSF) is recommended in cases of suspected blastomycosis involving the central nervous system.

**Reference Values:** Negative


Bleeding Diathesis Profile, Limited

**Clinical Information:** Bleeding problems may be associated with a wide variety of coagulation abnormalities or may be due to problems not associated with coagulation (trauma and surgery as obvious examples). A partial listing of causes follows. -Deficiency or functional abnormality (congenital or
acquired) of any of the following coagulation proteins: fibrinogen (factor I), factor II (prothrombin),
factor V, factor VII, factor VIII (hemophilia A), factor IX (hemophilia B), factor X, factor XI (hemophilia
C; bleeding severity not always proportionate to factor level), factor XIII (fibrin-stabilizing factor), von
Willebrand factor (VWF antigen and activity), and alpha-2 plasmin inhibitor and plasminogen activator
inhibitor (PAI-I; severe deficiency in rare cases). Neither alpha-2 plasmin inhibitor nor PAI-I are included
as a routine bleeding diathesis assay component, but either can be performed if indicated or requested.
-Deficiency (thrombocytopenia) or functional abnormality of platelets such as congenital (Glanzmann
thrombasthenia, Bernard-Soulier syndrome, storage pool disorders, etc) and acquired (myeloproliferative
disorders, uremia, drugs, etc) disorders. Platelet function abnormalities cannot be studied on mailed-in
specimens. -Specific factor inhibitors (most commonly directed against factor VIII); factor inhibitors
occur in 10% to 15% of the hemophilia population and are more commonly associated with severe
deficiencies of factor VIII or IX (antigen <1%). The inhibitor appears in response to transfusion therapy
with factor concentrates with no correlation of occurrence and amount of therapy. Factor VIII inhibitors
may occur spontaneously in the postpartum patient, with certain malignancies, in association with
autoimmune disorders (eg, rheumatoid arthritis, systemic lupus erythematosus), in the elderly, and for no
apparent reason. -Other acquired causes of increased bleeding include paraproteinemia; other
factor-specific inhibitors, including those against factor V, factor XI; or virtually any of the coagulation
proteins. -Acute disseminated intravascular coagulation/intravascular coagulation and fibrinolysis
(DIC/ICF), which is a fairly common cause of bleeding. Bleeding can also occur in patients with chronic
ICF.

**Useful For:** Detection of the more common potential causes of abnormal bleeding (eg, factor
deficiencies/hemophilia, von Willebrand disease, factor-specific inhibitors) and a simple screen to
evaluate for an inhibitor or severe deficiency of factor XIII (rare).

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:** Boender J, Kruip MJ, Leebeek FW: A Diagnostic Approach to Mild
Jun 27

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**Blomia tropicalis, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE
antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
immune response to allergens that may be associated with allergic disease. The allergens chosen for
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and
clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of
sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and
wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Aiding in the diagnosis of an allergic disease and defining the allergens responsible for
eliciting signs and symptoms. Identifying allergens that may be responsible for allergic disease and/or
anaphylactic episode, confirming sensitization to particular allergens prior to beginning immunotherapy,
and investigating the specificity of allergic reactions to insect venom allergens, drugs, or chemical
allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with
the concentration of IgE antibodies expressed as a class score or kU/L.
Reference Values:
Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
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4  17.5-49.9  Strongly positive
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6  > or =100  Strongly positive Reference values apply to all ages.


Blood Urea Nitrogen (BUN), Serum
Clinical Information: Urea is the final degradation product of protein and amino acid metabolism. In protein catabolism, the proteins are broken down to amino acids and deaminated. The ammonia formed in this process is synthesized to urea in the liver. This is the most important catabolic pathway for eliminating excess nitrogen in the human body. Increased blood urea nitrogen (BUN) may be due to prerenal causes (cardiac decompensation, water depletion due to decreased intake and excessive loss, increased protein catabolism, and high protein diet), renal causes (acute glomerulonephritis, chronic nephritis, polycystic kidney disease, nephrosclerosis, and tubular necrosis), and postrenal causes (eg, all types of obstruction of the urinary tract, such as stones, enlarged prostate gland, tumors). The determination of serum BUN currently is the most widely used screening test for the evaluation of kidney function. The test is frequently requested along with the serum creatinine test since simultaneous determination of these 2 compounds appears to aid in the differential diagnosis of prerenal, renal and postrenal hyperuremia.

Useful For: Screening test for evaluation of kidney function

Interpretation: Serum blood urea nitrogen (BUN) determinations are considerably less sensitive than BUN clearance (and creatinine clearance) tests, and levels may not be abnormal until the BUN clearance has diminished to less than 50%. Clinicians frequently calculate a convenient relationship, the urea nitrogen:creatinine ratio-serum bun in mg/dL/serum creatinine in mg/dL. For a normal individual on a normal diet, the reference interval for the ratio ranges between 12 and 20, with most individuals being between 12 and 16. Significantly lower ratios denote acute tubular necrosis, low protein intake, starvation, or severe liver disease. High ratios with normal creatinine levels may be noted with catabolic states of tissue breakdown, prerenal azotemia, high protein intake, etc. High ratios associated with high creatinine concentrations may denote either postrenal obstruction or prerenal azotemia superimposed on renal disease. Because of the variability of both the BUN and creatinine assays, the ratio is only a rough guide to the nature of the underlying abnormality. Its magnitude is not tightly regulated in health or disease and should not be considered an exact quantity.

Reference Values:
Males
1-17 years: 7-20 mg/dL
> or =18 years: 8-24 mg/dL
Reference values have not been established for patients who are <12 months of age.

Females
1-17 years: 7-20 mg/dL
Blood Urea Nitrogen, Body Fluid

**Clinical Information:** Serous and drain fluids: Peritoneal, abdominal drain, pleural, and thoracic drain Disruption of the urinary tract with subsequent leakage of urine into body cavities may be considered on the differential diagnosis when body fluid effusions of unknown origin develop. Elevated concentrations may elicit a more focused radiologic examination to identify possible bladder rupture or perforation or the development of urinary fistula, which are typically corrected by surgical intervention. Peritoneal dialysis fluid: Peritoneal dialysis (PD) is a type of dialysis in which hyperosmotic fluid is passed into the patient's peritoneal cavity for a prescribed dwell time, wherein the peritoneum is employed as the dialysis membrane. The dwell fluid containing waste molecules removed by dialysis is drained and replaced with fresh fluid and the process repeated. Measurements of urea, creatinine, glucose, or other electrolytes in serum, urine, and the peritoneal dialysate fluid aid in the assessment of peritoneal membrane transport characteristics and serve as markers of dialysis adequacy. Adequacy of PD is important to monitor because patients who maintain a sufficient clearance over time have longer survival. Kt/V is calculated to measure solute clearance from the daily peritoneal urea clearance (Kt), and the volume of distribution of urea (V). Adequacy and membrane transport characteristics are calculated by plugging in the appropriate laboratory parameters into software packages used by dialysis centers.

**Useful For:** Serous and drain fluids: Detecting the presence of urine in body fluid specimens
Peritoneal dialysis fluid: Assessing adequacy of peritoneal dialysis treatment protocols

**Interpretation:** For serous and drain fluids a fluid urea nitrogen to serum BUN (blood urea nitrogen) ratio above 1 is suggestive of the presence of urine in body fluids. Peritoneal dialysis fluid assessment is provided by the dialysis software.

**Clinical References:**

Blood Worm, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to
identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


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**BLOMP 35366**

**Bloom Syndrome, Mutation Analysis, 2281 delATCTGAinsTAGATTC (2281del6/ins7)**

**Clinical Information:** Bloom syndrome is characterized by short stature, sun sensitivity, susceptibility to infections, and a predisposition to cancer. Mutations in the BLM gene lead to genetic instability (increased chromosomal breakage and sister chromatid exchange) and cause the clinical manifestations of the syndrome. The protein encoded by the BLM gene is a helicase involved in maintaining DNA integrity. The carrier rate in the Ashkenazi Jewish population is 1 in 107. There is a common mutation in the Ashkenazi Jewish population: 2281delATCTGAins TAGATTC (2281del6/ins7). The carrier detection rate for this mutation is above 99%.

**Useful For:** Carrier screening for Bloom syndrome in individuals of Ashkenazi Jewish ancestry Confirmation of suspected clinical diagnosis of Bloom syndrome in individuals of Ashkenazi Jewish ancestry Prenatal diagnosis for Bloom syndrome in at-risk pregnancies

**Interpretation:** An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided.


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**MUSS 82548**

**Blue Mussel, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE
antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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**Blueberry IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**Blueberry, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**BOB1 Immunostain, Technical Component Only**

**Clinical Information:**
BOB.1/OBF.1 is a transcriptional coactivator that interacts with the transcription factors Oct1 or Oct2 in regulating transcription of immunoglobulin genes. In normal tonsil, the germinal center B cells all express BOB.1, while only scattered cells in the mantle zone express this protein. On immunohistochemistry, there is strong nuclear staining and weak cytoplasmic staining. Expression of BOB.1/OBF.1, Oct2, and PU.1 transcription factors are often down-regulated in classical Hodgkin lymphomas, in contrast to many cases of nodular lymphocyte-predominant Hodgkin lymphoma. This property can be useful in the diagnosis of lymphoma.

**Useful For:**
Classification of lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Bone Alkaline Phosphatase, Serum**

**Clinical Information:**
Bone alkaline phosphatase (BAP) is the bone-specific isoform of alkaline phosphatase. A glycoprotein that is found on the surface of osteoblasts, BAP reflects the biosynthetic activity of these bone-forming cells. BAP has been shown to be a sensitive and reliable indicator of bone metabolism. Normal bone is constantly undergoing remodeling in which bone degradation or
Resorption is balanced by bone formation. This process is necessary for maintaining bone health. If the process becomes uncoupled and the rate of resorption exceeds the rate of formation, the resulting bone loss can lead to osteoporosis and, consequently, a higher susceptibility to fractures. Osteoporosis is a metabolic bone disease characterized by low bone mass and abnormal bone microarchitecture. It can result from a number of clinical conditions including states of high bone turnover, endocrine disorders (primary and secondary hyperparathyroidism and thyrotoxicosis), osteomalacia, renal failure, gastrointestinal diseases, long-term corticosteroid therapy, multiple myeloma, and cancer metastatic to the bones. Paget disease is another common metabolic bone disease caused by excessive rates of bone remodeling resulting in local lesions of abnormal bone matrix. These lesions can result in fractures or neurological involvement. Antiresorptive therapies are used to restore the normal bone structure.

**Useful For:** Diagnosis and assessment of severity of metabolic bone disease including Paget disease, osteomalacia, and other states of high bone turnover Monitoring efficacy of antiresorptive therapies including postmenopausal osteoporosis treatment

**Interpretation:** Bone alkaline phosphatase (BAP) concentration is high in Paget disease and osteomalacia. Antiresorptive therapies lower BAP from baseline measurements in Paget disease, osteomalacia, and osteoporosis. Several studies have shown that antiresorptive therapies for management of osteoporosis patients should result in at least a 25% decrease in BAP within 3 to 6 months of initiating therapy. (2,3) BAP also decreases following antiresorptive therapy in Paget disease. (4) When used as a marker for monitoring purposes, it is important to determine the critical difference (or least significant change). The critical difference is defined as the difference between 2 determinations that may be considered to have clinical significance. The critical difference for this method was calculated to be 25% with a 95% confidence level. (1)

**Reference Values:**

**Males**
- <2 years: 25-221 mcg/L
- 2-9 years: 27-148 mcg/L
- 10-13 years: 35-169 mcg/L
- 14-17 years: 13-111 mcg/L
- Adults: < or =20 mcg/L

**Females**
- <2 years: 28-187 mcg/L
- 2-9 years: 31-152 mcg/L
- 10-13 years: 29-177 mcg/L
- 14-17 years: 7-41 mcg/L
- Adults
  - Premenopausal: < or =14 mcg/L
  - Postmenopausal: < or =22 mcg/L

**Clinical References:**

**Bone Histomorphometry, Consultant Interpretation, Slides Only**

**Clinical Information:** Bone histomorphometry is a very sophisticated procedure utilizing full thickness bone biopsy. Techniques such as 2-time interval labeling with tetracycline permit the direct measurement of the rate of bone formation. The information derived is useful in the diagnosis of metabolic bone diseases including renal osteodystrophy, osteomalacia, and osteoporosis. Other obtainable information relate to disorders such as aluminum toxicity and iron abnormalities.
Useful For: Identifying undetermined metabolic bone disease in submitted slide specimens
Diagnosing renal osteodystrophy Diagnosing osteomalacia Diagnosing osteoporosis Diagnosing Paget
disease Assessing the effects of therapy Identifying disorders of the hematopoietic system Diagnosing
aluminum toxicity Identifying the presence of iron in the bone

Interpretation: Clinical endocrinologists trained in histomorphometric techniques review and
interpret the histological appearance. A pathologist interprets the bone marrow from a hematoxylin and
eosin-stained slide. No histomorphometric values are given.

Reference Values:
The laboratory will provide an interpretive report.

Clinical References: Recker RR: Bone Histomorphometry: Techniques and Interpretation. Boca
Raton, FL, CRC Press, 1983

### BHISC 70312

**Bone Histomorphometry, Gross Microscopic Exam**

**Clinical Information:** Bone histomorphometry is a very sophisticated procedure utilizing
full-thickness bone biopsy. Techniques such as 2-time interval labeling with tetracycline permit the
direct measurement of the rate of bone formation. The information derived is useful in the diagnosis of
metabolic bone diseases, including renal osteodystrophy, osteomalacia, and osteoporosis, and other
disorders such as aluminum toxicity and iron abnormalities.

**Useful For:** Undetermined metabolic bone disease in wet tissue specimens Renal osteodystrophy
Osteomalacia Osteoporosis Paget disease Assessing effects of therapy Identification of some disorders
of the hematopoietic system Aluminum toxicity Presence of iron in the bone

**Interpretation:** Computer-generated histomorphometric values are given for adequate specimens.
Normal histomorphometric values for iliac crest are provided (female only). An interpretive report is
provided.

**Reference Values:**
The laboratory will provide a quantitative and an interpretive report.

**Clinical References:** Recker RR: Bone Histomorphometry: Techniques and Interpretation. Boca
Raton, FL, CRC Press, 1983

### BMAPC 113350

**Bone Marrow Aspirate (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

### BMBPC 113351

**Bone Marrow Biopsy (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

### BMCPC 113352

**Bone Marrow Clot (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.
Bordetella pertussis and Bordetella parapertussis, Molecular Detection, PCR

Clinical Information: Bordetella pertussis is the highly contagious etiological agent of pertussis or whooping cough. Bordetella parapertussis causes a similar, but generally less severe illness. Despite vaccination efforts, B pertussis remains common in the United States, underscoring the need for effective diagnostic tests. In the United States, pertussis is most common in the late summer months. Pertussis vaccination does not prevent B parapertussis infection, which generally occurs in a younger age group than disease caused by B pertussis. Diagnosis of pertussis is based on having a high clinical index of suspicion for the infection, along with confirmation by laboratory testing. Laboratory testing methods include nucleic acid amplification tests (eg, PCR), serology, culture and direct fluorescent antibody testing. Culture and direct fluorescent antibody testing are limited by low sensitivity, rendering nucleic acid amplification tests and serology the tests of choice. The Centers for Disease Control and Prevention recommends PCR testing for patients suspected of having acute pertussis. B pertussis PCR detects roughly twice as many cases as culture. B pertussis DNA can be detected up to 4 weeks, or longer (up to 8 weeks in our experience)(1) after symptom onset. However, over time, the amount of B pertussis and B parapertussis DNA will diminish, rendering the assay less sensitive. A serologic response to B pertussis is typically mounted by 2 weeks following infection and, therefore, detection of IgG-class antibodies to pertussis toxin (PT), which is only produced by B pertussis, can be a useful adjunct for diagnosis at later stages of illness at a time when the amount of B pertussis may be below the limit of detection of the PCR assay.

Useful For: Preferred diagnostic test for the detection of Bordetella pertussis or Bordetella parapertussis

Interpretation: A positive result indicates the presence of DNA from Bordetella pertussis or B parapertussis. In some cases, a patient may test positive for both B pertussis and B parapertussis. Cross-reactivity with B holmesii and B bronchiseptica may occur with the B pertussis assay (see Cautions). A negative result indicates the absence of detectable B pertussis and B parapertussis DNA in the specimen but does not negate the presence of organism or active or recent disease (known inhibition rate of <1%) and may occur due to inhibition of PCR, sequence variability underlying primers and/or probes, or the presence of B pertussis or B parapertussis in quantities less than the limit of detection of the assay. Additionally, patients presenting late after symptom onset may test negative; in such cases, testing for B pertussis antibody, IgG, in serum may be considered.

Reference Values: Not applicable


Bordetella pertussis Antibody, IgG, Serum

Clinical Information: Bordetella pertussis, the causative agent of whooping cough, is highly contagious and remains endemic in the United States despite the high rate of vaccination. Acute Bordetella pertussis infections are typically diagnosed by culture or nucleic acid amplification testing (NAAT). However, symptomatic adults and adolescents often seek medical attention later in the course of infection, at which time the sensitivity of these 2 methods to detect the infectious agent decreases. A serologic response to Bordetella pertussis is typically mounted at 2 weeks following infection, and therefore detection of IgG-class antibodies to pertussis toxin (PT), which is only produced by Bordetella pertussis, can be a useful adjunct for diagnosis at later stages of illness. Prior to testing, providers should review whether the patient was recently vaccinated using the Tdap (Tetanus-Diphtheria-acellular...
Pertussis) or DTaP vaccines. The acellular pertussis vaccine contains 1 to 5 Bordetella pertussis antigens, including filamentous hemagglutinin, pertactin, 2 fimbrial agglutinogens, and significant levels of PT. Therefore, recent vaccination for Bordetella pertussis, specifically within the last 2 to 6 months, may lead to a positive result by the anti-PT IgG assay and knowledge of the patient's vaccination history is important for accurate result interpretation.

**Useful For:** Diagnosis of recent infection with Bordetella pertussis in patients with > or =2 weeks of symptoms consistent with whooping cough

**Interpretation:** Negative (<40 IU/mL): No IgG antibodies to pertussis toxin (PT) detected. Results may be falsely negative in patients with <2 weeks of symptoms. Borderline (40-<100 IU/mL): Recommend follow-up testing in 10 to 14 days if clinically indicated. Positive (> or =100 IU/mL): IgG antibodies to pertussis toxin (PT) detected. Results suggest recent infection with or recent vaccination against Bordetella pertussis.

**Reference Values:**
- > or =100 IU/mL (positive)
- > or = 40-<100 IU/mL (borderline)
- <40 IU/mL (negative)

**Clinical References:**
Borrelia miyamotoi Detection PCR, Spinal Fluid

Clinical Information: Borrelia miyamotoi is a spirochetal bacterium that is closely related to the Borrelia species that cause tick-borne relapsing fever (TBRF), and it is more distantly related to the Borrelia species that cause Lyme disease. This organism causes a febrile illness like TBRF, with body and join pain, fatigue, and rarely, rash, and has been detected in Ixodes scapularis and I pacificus ticks. These ticks are also the vectors for Lyme disease, anaplasmosis, and babesiosis. The preferred method for detecting B miyamotoi is real-time PCR. Less sensitive and specific methods for detecting B miyamotoi and agents of TBRF include identification of spirochetes in peripheral blood films and cerebrospinal fluid (CSF) preparations and serologic testing. This assay does not detect the Borrelia species that cause Lyme disease.

Useful For: Aids in the diagnosis of Borrelia miyamotoi infection in conjunction with clinical findings

Interpretation: A positive result indicates the presence of Borrelia miyamotoi DNA and is consistent with active or recent infection. While positive results are highly specific indicators of disease, they should be correlated with symptoms and clinical findings of tick-borne relapsing fever.

Reference Values:
Negative


Botrytis cinerea, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
### Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
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<tbody>
<tr>
<td>0</td>
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<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
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<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>≥ 100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

*Reference values apply to all ages.*

### Clinical References:


### Bovine Serum Albumin, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</table>
Box Elder/Maple, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>Strongly positive Reference values apply to all ages.</td>
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Brachyury Immunostain, Technical Component Only

Clinical Information: Brachyury expression is required for the specification of mesodermal identity, representing one of the key genes regulating notochord formation. The brachyury gene, a T-box
transcription factor, is uniquely expressed in chordomas.

**Useful For:** Aids in identifying chordomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**BBRAF 35893**

**BRAF Analysis (Bill Only)**

**Reference Values:**
- This test is for billing purposes only.
- This is not an orderable test.

**BRAFC 35372**

**BRAF Mutation Analysis (V600), Melanoma**

**Clinical Information:** Assessment for BRAF V600 mutations has clinical utility in that it is a predictor of response to antmutant BRAF therapy. BRAF is a member of the mitogen-activated protein/extracellular signal-regulated (MAP/ERK) kinase pathway, which plays a role in cell proliferation and differentiation. Dysregulation of this pathway is a key factor in tumor progression. Targeted therapies directed to components of this pathway have demonstrated some success with increases both in progression-free and overall survival in patients with certain tumors. Effectiveness of these therapies, however, depends in part on the mutation status of the pathway components. Malignant melanoma, one of the most aggressive forms of skin cancer, has a high frequency of BRAF mutations. Approximately 44% to 70% of melanoma cases have a BRAF mutation, and of those, approximately 50% to 90% are the V600E mutation. Current data suggest that the efficacy of BRAF-targeted therapies in melanoma is confined to patients with tumors with activating BRAF mutations, such as V600E, which leads to increased activation of the kinase pathway. While this test was designed to evaluate for the V600E alteration, cross-reactivity with other alterations at the V600 codon have been described. At this time, this test is approved specifically for melanoma tumors. Please refer to BRAFT / BRAF Mutation Analysis (V600E), Tumor for BRAF testing in nonmelanoma tumors.

**Useful For:** Identification of melanoma tumors that may respond to BRAF-targeted therapies

**Interpretation:** An interpretative report will be provided.

BRAF Mutation Analysis (V600E), Tumor

Clinical Information: Hereditary nonpolyposis colon cancer (HNPCC), also known as Lynch syndrome, is an inherited cancer syndrome caused by a germline mutation in 1 of several genes involved in DNA mismatch repair (MMR), including MLH1, MSH2, MSH6 and PMS2. There are several laboratory-based strategies that help establish the diagnosis of HNPCC/Lynch syndrome, including testing tumor tissue for the presence of microsatellite instability (MSI-H) and loss of protein expression for any 1 of the MMR proteins by immunohistochemistry (IHC). It is important to note, however, that the MSI-H tumor phenotype is not restricted to inherited cancer cases; approximately 20% of sporadic colon cancers are MSI-H. Thus, MSI-H does not distinguish between a somatic (sporadic) and a germline (inherited) mutation, nor does it identify which gene is involved. Although IHC analysis is helpful in identifying the responsible gene, it also does not distinguish between somatic and germline defects. Defective MMR in sporadic colon cancer is most often due to an abnormality in MLH1, and the most common cause of gene inactivation is promoter hypermethylation (epigenetic silencing). A specific mutation in the BRAF gene (V600E) has been shown to be present in approximately 70% of tumors with hypermethylation of the MLH1 promoter. Importantly, the V600E mutation has not been identified to date in cases with germline MLH1 mutations. Thus, direct assessment of MLH1 promoter methylation status and testing for the BRAF V600E mutation can be used to help distinguish between a germline mutation and epigenetic/somatic inactivation of MLH1. Tumors that have the BRAF V600E mutation and demonstrate MLH1 promoter hypermethylation are almost certainly sporadic, whereas tumors that show neither are most often caused by an inherited mutation. Although testing for the BRAF V600E mutation and MLH1 promoter hypermethylation are best interpreted together, they are also available separately to accommodate various clinical situations and tumor types. These tests can provide helpful diagnostic information when evaluating an individual suspected of having HNPCC/Lynch syndrome, especially when testing is performed in conjunction with MSIHC / Microsatellite Instability (MSI)/Immunohistochemistry (IHC) Profile-Lynch/Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Screen, which includes MSI and IHC studies. It should be noted that these tests are not genetic tests, but rather stratify the risk of having an inherited cancer predisposition and identify patients who might benefit from subsequent genetic testing. See Lynch Syndrome Testing Algorithm in Special Instructions.

Assessment for the BRAF V600E mutation has alternative clinical utilities. BRAF is part of the epidermal growth factor receptor (EGFR) signaling cascade, which plays a role in cell proliferation. Dysregulation of this pathway is a key factor in tumor progression. Targeted therapies directed to components of this pathway have demonstrated some success (increased progression-free and overall survival) in treating patients with certain tumors. Effectiveness of these therapies, however, depends in part on the mutation status of the pathway components.

Useful For: An adjunct to MSIHC / Microsatellite Instability (MSI)/Immunohistochemistry (IHC) Profile-Lynch/Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Screen, when colon tumor demonstrates microsatellite instability (MSI-H) and loss of MLH1 protein expression, to help distinguish a somatic versus germline event prior to performing expensive germline testing. An adjunct to negative MLH1 germline testing in cases where colon tumor demonstrates MLH1 protein expression, to help distinguish a somatic versus germline event prior to performing expensive germline testing. An adjunct to negative MLH1 germline testing An adjunct to negative MLH1 germline testing An adjunct to negative MLH1 germline testing An adjunct to negative MLH1 germline testing An adjunct to negative MLH1 germline testing An adjunct to negative MLH1 germline testing An adjunct to negative MLH1 germline testing An adjunct to negative MLH1 germline testing. Note: Mayo's preferred screening test (BRMLH / MLH1 Hypermethylation and BRAF Mutation Analyses, Tumor) includes both MLH1 promoter hypermethylation and BRAF V600E testing. To identify colon tumors with a previously negative KRAS mutation analysis result that may respond to epidermal growth factor receptor-targeted therapies. To identify melanoma tumors that may respond to anti-BRAF targeted therapies. Note: This is a laboratory developed test and has not been FDA-approved for this purpose.

Interpretation: An interpretive report will be provided.
**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

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**BRAFV**

**BRAF V600E Immunostain, Technical Component Only**

**Clinical Information:**
BRAF is a serine/threonine protein kinase and a member of the Raf family. The BRAF V600E mutation leads to constitutive activation of the mitogen activated protein kinase pathway, which plays a role in cell proliferation and tumorigenesis. This mutation has been detected in a variety of tumors such as melanoma, colorectal cancer, papillary thyroid carcinoma, hairy cell leukemia, Langerhans cell histiocytosis, and pleomorphic xanthoastrocytomas.

**Useful For:** Identification of BRAF V600E-mutated protein

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**BRAZ**

**Brazil Nut, IgE**

**Clinical Information:**
Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and...
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**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**BRAJ3**

**BRCA1/BRCA2 Ashkenazi Jewish 3-Site Mutation Panel**

**Clinical Information:** Hereditary breast and ovarian cancer (HBOC) is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the BRCA1 or BRCA2 genes. Mutations within these 2 genes account for the majority of hereditary breast and ovarian cancer families. HBOC is predominantly characterized by young-onset breast cancer and ovarian cancer. However, HBOC is also associated with increased risks for prostate cancer, pancreatic cancer, fallopian tube cancer, and male breast cancer. HBOC is highly penetrant; the risk for developing an invasive breast cancer is about 60% to 65% and the risk for developing ovarian cancer is about 40% by age 70. Some individuals develop multiple primary or bilateral cancers. The National Comprehensive Cancer Network and the American Cancer Society provide recommendations regarding the medical management of individuals with HBOC. There are founder mutations in BRCA1 and BRCA2 described in several populations including the Dutch, Icelandic, and Ashkenazi Jewish populations. The 3 common founder mutations in the Ashkenazi Jewish population are c.68_69delAG and c.5266dupC in BRCA1, and c.5946delT in BRCA2. These are listed according to current Human Genome Variation Society guidelines; however, these are also well-known by their previous nomenclature: c.185delAG and c.5385insC in BRCA1, and c.6174delT in BRCA2. The overall prevalence of the BRCA1/2 founder mutations in the Ashkenazi Jewish population is 1 in 40. Per the National Comprehensive Cancer Network, women of Ashkenazi Jewish ancestry who have been diagnosed with breast or ovarian cancer should be considered for testing for the 3 common founder mutations (www.nccn.org).
Useful For: Establishing a diagnosis of hereditary breast and ovarian cancer (HBOC) in patients of Ashkenazi Jewish ancestry

Interpretation: An interpretive report is provided. All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


BRCA1/BRCA2 Genes, Full Gene Analysis

Clinical Information: Hereditary breast and ovarian cancer (HBOC) is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the BRCA1 or BRCA2 genes. Mutations within these 2 genes account for the majority of hereditary breast and ovarian cancer families. HBOC is predominantly characterized by young-onset breast cancer and ovarian cancer. However, HBOC is also associated with increased risks for prostate cancer, pancreatic cancer, fallopian tube cancer, and male breast cancer. HBOC is highly penetrant; the risk for developing an invasive breast cancer is about 60% to 65% and the risk for developing ovarian cancer is about 40% by age 70. Some individuals develop multiple primary or bilateral cancers. The National Comprehensive Cancer Network and the American Cancer Society provide recommendations regarding the medical management of individuals with HBOC. There are founder mutations in BRCA1 and BRCA2 described in several populations including the Dutch, Icelandic, and Ashkenazi Jewish populations. The 3 common founder mutations in the Ashkenazi Jewish population are c.185delAG and c.5385insC in BRCA1, and c.6174delT in BRCA2.

Useful For: Establishing a diagnosis of hereditary breast and ovarian cancer (HBOC) Identification of familial BRCA1 or BRCA2 mutation to allow for predictive testing in family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.

C2729
Breast Carcinoma-Associated Antigen (CA 27.29), Serum

Clinical Information: Carcinoma of the breast is the most prevalent form of cancer in women. These tumors often produce mucinous antigens that are large-molecular-weight glycoproteins with O-linked oligosaccharide chains. Monoclonal antibodies directed against these antigens have been developed, and several immunoassays are available to quantitate the levels of tumor-associated mucinous antigens in serum. The antibodies recognize epitopes of a breast cancer-associated antigen encoded by the human mucin 1 (MUC-1) gene, which is known by several names including MAM6, milk mucin antigen, CA 27.29, and cancer antigen 15-3 (CA 15-3). While CA 27.29 is expressed at the apical surface of normal epithelial cells, it is present throughout malignant epithelial cells of the breast, lung, ovary, pancreas, and other sites. The cancer-associated form of the antigen is less extensively glycosylated than the normal form and more specific for tumor cells.

Useful For: FDA-approved cancer-associated antigen (CA 27.29) for serial testing in women with prior stage II or III breast cancer who are clinically free of disease Predicting early recurrence of disease in women with treated carcinoma of the breast As an indication that additional tests or procedures should be performed to confirm recurrence of breast cancer

Interpretation: Increased levels of cancer-associated antigen (CA 27.29) (>38 U/mL) may indicate recurrent disease in a woman with treated breast carcinoma.

Reference Values:
Males
> or =18 years: < or =38.0 U/mL (use not defined)
Females
> or =18 years: < or =38.0 U/mL
Reference values have not been established for patients who are <18 years of age. Serum markers are not specific for malignancy, and values may vary by method.


BRG1
BRG1 (SMARCA4), Immunostain, Technical Component Only

Clinical Information: BRG1 (formal name: SMARCA4) is a member of the switch/sucrose nonfermentable (SWI/SNF) chromatin remodeling complex. Biallelic mutations in BRG1 have been reported in ovarian small cell carcinoma of hypercalcemic type (SCCOHT) amongst other tumors. Tumors with these mutations demonstrate a loss of BRG1 protein expression in the nucleus. SCCOHT is difficult to diagnose and loss of BRG1 expression can help in differentiating SCCOHT from its mimics including other primary or metastatic tumors of the ovaries.

Useful For: Diagnosing ovarian small cell carcinoma of hypercalcemic type (SCCOHT)

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation.
for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**BRBPS 65058**

**Broad Range Bacterial PCR and Sequencing**

**Clinical Information:** Cultures from patients with suspected bacterial infection involving normally sterile sites may fail to provide bacterial (including mycobacterial) growth for identification due to the presence of a fastidious or slow-growing bacterium or as a result of antecedent antimicrobial chemotherapy. Broad-range bacterial PCR amplification followed by Sanger sequencing of the amplified product may potentially detect bacterial (including mycobacterial) nucleic acids in such situations, enabling a diagnosis. Ideal specimens are those in which bacteria (includes mycobacteria) are visualized by microscopy. Heart valves from patients with endocarditis with positive Gram stains are, for example, especially suitable.

**Useful For:** Detecting and identifying bacteria (including mycobacteria) from normally sterile sources, including synovial fluid; body fluids such as pleural, peritoneal and pericardial fluids, cerebrospinal fluid (CSF); and both fresh and formalin-fixed paraffin-embedded (FFPE) tissues

**Interpretation:** A positive broad-range PCR/sequencing result indicates that bacterial nucleic acid of the specified organisms was detected, which may be due to bacterial infection or environmental or contaminating nucleic acids in the specimen. A negative broad-range PCR/sequencing result indicates the absence of detectable bacterial (including mycobacterial) nucleic acids in the specimen, but does not rule-out false-negative results that may occur due to sampling error, sequence variability underlying the primers, the presence of bacterial nucleic acids in quantities less than the limit of detection of the assay, or inhibition of PCR. If PCR testing appears to be negative but there is evidence of PCR inhibition, testing will be repeated. If inhibition is again detected, the result will be reported as "PCR inhibition present."

**Reference Values:**
No bacterial DNA detected


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**FBRCG 57642**

**Broccoli IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:** <2 mcg/mL.

**Clinical References:**
The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

### Broccoli, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.

immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>4</td>
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**Brucella Antibody Screen, IgG and IgM, Serum**

**Clinical Information:** Worldwide, brucellosis remains a major disease in humans and domesticated animals. Brucella infects goats (B melitensis), cattle (B abortus), swine (B suis), and dogs (B canis).(1) The disease has a limited geographic distribution. Few cases occur in the United States, with the bulk occurring in the Mediterranean region, Western Asia, and parts of Latin America and Africa. Three species of Brucella commonly cause disease in humans: B melitensis, B suis, and B abortus. The acute disease often presents with fever, chills, and malaise; the chronic form also causes abscesses in bone, brain, spleen, liver, and kidney.

**Useful For:** Evaluating patients with suspected brucellosis

**Interpretation:** In the acute stage of the disease there is an initial production of IgM antibodies, followed closely by production of IgG antibodies. IgG-class antibodies may decline after treatment; however, high levels of circulating IgG-class antibodies may be found without any active disease. Chronic brucellosis shows a predominance of IgG-class antibodies with little or no detectable IgM. Rising levels of specific antibody in paired sera can be regarded as serological evidence of recent infection. The presence of specific IgM in a single specimen may also indicate a recent infection,
although IgM-class antibodies may persist for months following acute disease. The CDC recommends that specimens testing positive for IgG or IgM by enzyme-linked immunosorbent assay (ELISA) be confirmed by a Brucella-specific agglutination method.(2) The CDC/Council of State and Territorial Epidemiologists case definition for human brucellosis states that the laboratory criteria for diagnosis includes 1) Isolation of Brucella species from a clinical specimen, 2) Four-fold or greater rise in Brucella agglutination titer between acute- and convalescent-phase serum specimens obtained more than 2 weeks apart and studied at the same laboratory, or 3) Demonstration by immunofluorescence of Brucella species in a clinical specimen. Positive results by ELISA that are not confirmed by Brucella-specific agglutination may represent false-positive screening results. If clinically indicated, a new specimen should be tested after 7 to 14 days. If results of ELISA are negative and a recent infection is suspected, a new specimen should be tested after 7 to 14 days.

**Reference Values:**

**IgG SCREEN**

Negative (reported as positive, negative, or equivocal)

**IgM SCREEN**

Negative (reported as positive, negative, or equivocal)

**Clinical References:**


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### Brucella Culture

**Clinical Information:** Brucella species are facultative intracellular Gram-negative staining bacilli capable of producing the disease "brucellosis" in humans. Human disease likely is acquired by contact with animals infected with the organism (Brucella abortus, B suis, B melitensis, and occasionally B canis) either by direct contact or by ingestion of meat or milk. The signs and symptoms associated with brucellosis may include fever, night sweats, chills, weakness, malaise, headache, and anorexia. The physical examination may reveal lymphadenopathy and hepatosplenomegaly. A definitive diagnosis of brucellosis is made by recovering the organism from blood, fluid (including urine), or tissue specimens.

**Useful For:** Diagnosis of brucellosis

**Interpretation:** Isolation of a Brucella species indicates infection. Cultures of blood and/or bone marrow are positive in 70% to 90% of acute Brucella infections, but much less so in subacute or chronic infections. In these latter instances, culture yield is highest from the specific tissue involved, or serology may be necessary to establish diagnosis.

**Reference Values:**

No growth after 14 days

**Clinical References:**


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### Brucella Culture, Blood

**Clinical Information:** Brucella species are facultative intracellular Gram-negative-staining bacilli capable of producing the disease "brucellosis" in humans. Human disease likely is acquired by contact
with animals infected with the organism (Brucella abortus, B suis, B melitensis, and occasionally B canis) either by direct contact or by ingestion of meat or milk. The signs and symptoms associated with brucellosis may include fever, night sweats, chills, weakness, malaise, headache, and anorexia. The physical examination may reveal lymphadenopathy and hepatosplenomegaly. A definitive diagnosis of brucellosis is made by recovering the organism from blood, fluid (including urine), or tissue specimens.

**Useful For:** Diagnosis of brucellosis in blood specimens

**Interpretation:** Isolation of a Brucella species indicates infection. Cultures of blood and/or bone marrow are positive in 70% to 90% of acute Brucella infections, but much less so in subacute or chronic infections. In these latter instances, culture yield is highest from the specific tissue involved, or serology may be necessary to establish diagnosis.

**Reference Values:**
No growth after 14 days

**Clinical References:**

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**BRUTA 8112**

**Brucella Total Antibody Confirmation, Agglutination, Serum**

**Clinical Information:** Brucella species are facultative intracellular, gram-negative staining bacilli capable of producing the disease "brucellosis" in humans. Human disease likely is acquired by contact with animals infected with the organism (B abortus, B suis, B melitensis, and occasionally B canis) either by direct contact or by ingestion of meat or milk. The signs and symptoms associated with brucellosis may include fever, night sweats, chills, weakness, malaise, headache, and anorexia. The physical examination may reveal lymphadenopathy and hepatosplenomegaly. A definitive diagnosis of brucellosis is made by recovering the organism from bone marrow, blood, fluid (including urine), or tissue specimens. In cases of suspected brucellosis, serology may assist in the diagnosis and play a supplementary role to routine culture. Antibodies to Brucella species may not become detectable until 1 to 2 weeks following the onset of symptoms, so serum specimens drawn during acute disease may be negative by serology in patients with brucellosis. If serology is performed, the CDC currently recommends that specimens testing positive or equivocal for IgG or IgM by a screening EIA be confirmed by a Brucella-specific agglutination method.(1)

**Useful For:** Evaluating patients with suspected brucellosis

**Interpretation:** The CDC recommends that specimens testing positive or equivocal for IgG or IgM by a screening EIA be confirmed by a Brucella-specific agglutination method.(1) Negative to a titer of 1:40 or higher can be seen in the normal, healthy population. A titer of 1:80 or greater is often considered clinically significant(2); however, a 4-fold or greater increase in titer between acute and convalescent phase sera is required to diagnose acute infection. The CDC/Council of State and Territorial Epidemiologists case definition for human brucellosis states that the laboratory criteria for diagnosis includes 1) Isolation of Brucella species from a clinical specimen, 2) Four-fold or greater rise in Brucella agglutination titer between acute- and convalescent-phase serum specimens drawn more than 2 weeks apart and studied at the same laboratory, or 3) Demonstration by immunofluorescence of Brucella species in a clinical specimen. Positive results by a screening EIA that are not confirmed by Brucella-specific agglutination may represent false-positive screening results. If clinically indicated, a new specimen should be tested after 7 to 14 days.

**Reference Values:**
<1:80

**Clinical References:**
2. Welch RJ, Litwin CM: A comparison of Brucella IgG and IgM ELISA assays with
Brugada Syndrome Multi-Gene Panel, Blood

Clinical Information: Brugada syndrome (BrS) is a genetic cardiac disorder characterized by ST segment elevation in leads V1-V3 on electrocardiography (EKG) with a high risk for ventricular arrhythmias that can lead to sudden cardiac death. BrS is inherited in an autosomal dominant manner and is caused by pathogenic variants in genes that encode cardiac ion channels. The diagnosis of BrS is established based on the characteristic EKG abnormality along with personal and family health history, and also requires exclusion of other causes including cardiac structural abnormalities, medications, and electrolyte imbalances. BrS has also been called sudden unexplained nocturnal death syndrome (SUNDS) due to the tendency for syncope and sudden cardiac death to occur at rest or during sleep. The most common presentation of BrS is a male in his 40s with a history of syncopal episodes and malignant arrhythmias. However, presentation may occur at any age including infancy, where BrS may present as SIDS (sudden infant death syndrome). Published studies indicate that BrS is responsible for 4% to 12% of unexpected sudden deaths and for up to 20% of all sudden death in individuals with a structurally normal heart. The prevalence of BrS in the general population is difficult to determine due to the challenges of diagnosing the condition. In Southeast Asia where SUNDS is endemic, the prevalence of BrS is estimated to be 1 in 2,000. Of note, men are 8 to 10 times more likely to express symptoms of BrS, but the disease affects females as well and both sexes are at risk for ventricular arrhythmia and sudden death.

Approximately 25% to 30% of BrS is accounted for by pathogenic variants in the genes known to cause the disorder, with the majority of cases attributed to the SCN5A gene. Although the majority of pathogenic variants identified to date have been detected by sequence analysis, large deletions in the SCN5A, SCN3B, CACNA1C, and KCNE3 genes have been reported in BrS. Genetic testing for BrS is supported by multiple consensus statements to confirm the diagnosis and identify at-risk family members. This is particularly important because the majority of patients with BrS are asymptomatic, but asymptomatic individuals may still be at increased risk for cardiac events. Pre- and posttest genetic counseling is an important factor in the diagnosis and management of BrS and is supported by expert consensus statements.

Useful For: Providing a genetic evaluation for patients with a personal or family history suggestive of Brugada syndrome (BrS) Establishing a diagnosis of a BrS, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying variants within genes known to be associated with increased risk for disease features and allowing for predictive testing of at-risk family members

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values:
An interpretive report will be provided.

Brussel Sprouts, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Bruton Tyrosine Kinase (BTK) Genotype and Protein Analysis, Full Gene Sequence and Flow Cytometry

**Clinical Information:** X-linked agammaglobulinemia (XLA) is a humoral primary immunodeficiency affecting males in approximately 1 in 200,000 live births. XLA is caused by variants in the Bruton tyrosine kinase gene (BTK),(1) which results in a profound block in B-cell development within the bone marrow and a significant reduction, or complete absence, of mature B cells in peripheral blood.(2) Approximately 85% of male patients with defects in early B-cell development have XLA.(3) Due to the lack of mature B cells, XLA patients have markedly reduced levels of all major classes of immunoglobulins in the serum and are, therefore, susceptible to severe and recurrent bacterial infections. Pneumonia, otitis media, enteritis, and recurrent sinopulmonary infections are among the key
clinical diagnostic characteristics of the disease. The spectrum of infectious complications also includes
enteroviral meningitis, septic arthritis, cellulitis, and empyema, among others. The disease typically
manifests in male children younger than 1 year of age. BTK, the only gene associated with XLA, maps
to the X-chromosome at Xq21.3-Xq22 and consists of 19 exons spanning 37.5 kb genomic DNA.(4)
BTK encodes a nonreceptor tyrosine kinase of the Btk/Tec family. The Bruton tyrosine kinase (Btk)
protein consists of 5 structural domains (PH, TH, SH3, SH2, and TK). Variants causing XLA have been
found in all domains of the BTK gene, as well as noncoding regions of the gene. Missense variants
account for 40% of all variants, while nonsense variants account for 17%, deletions 20%, insertions 7%,
and splice-site variants 16%. Over 600 unique variants in the BTK gene have been detected by full gene
sequencing and are listed in BTKbase, a database for BTK variants (http://bioinf.uta.fi/BTKbase).(5)
Genotype-phenotype correlations have not been completely defined for BTK, but it is clear that
nonsense variants are overrepresented 4-fold compared to substitutions, which indicates that the latter
may be tolerated without causing a phenotype. The type and location of the variant in the gene clearly
affects the severity of the clinical phenotype. Some variants manifest within the first year or 2 of life,
allowing an early diagnosis. Others present with milder phenotypes, resulting in diagnosis later in
childhood or in adulthood.(5) Delayed diagnoses can be partly explained by the variable severity of
XLA, even within families in which the same variant is present. While the disease is considered fully
penetrant, the clinical phenotype can vary considerably depending on the nature of the specific BTK
variant.(5) Lyonization of this gene is not typical and only 1 case of XLA in a female has been reported
so far due to skewed lyonization in a carrier female. Therefore, females with clinical features that are
identical to XLA should be evaluated for autosomal recessive agammaglobulinemia when deemed
clinically appropriate(6) and for XLA, if a male parent is affected with the disease. A flow cytometry
test for intracellular Btk in monocytes using an anti-Btk monoclonal antibody was developed by
Futatani et al, which was used to evaluate both XLA patients and carriers.(7) In this study, 41 unrelated
XLA families were studied and deficient Btk protein expression was seen in 40 of these 41 patients,
with complete Btk deficiency in 35 patients and partial Btk deficiency in 5 patients. One patient had a
normal level of Btk protein expression. The 6 patients with partial or normal Btk expression had
missense BTK variants. Additionally, the flow cytometry assay detected carrier status in the mothers of
35 of the 41 patients (approximately 85%). In the 6 patients where the Btk expression was normal in the
mothers of XLA patients, it was noted that all these patients were sporadic cases without previous
family history of the disease.(7) It appears, therefore, that most BTK variants result in deficient
expression of Btk protein, which can be detected by flow cytometry in monocytes.(7,8) Also, the
mosaic expression of Btk protein in the monocytes by flow cytometry is potentially useful in the
diagnosis of female carriers.(8) The flow cytometry test therefore provides a convenient screening tool
for the diagnosis of XLA with confirmation of the diagnosis by BTK genotyping.(7,8) In the rare patient
with the clinical features of XLA but normal Btk protein expression, BTK genotyping must be
performed to determine the presence of a variant. A diagnosis of XLA should be suspected in males
with 1) early-onset bacterial infections, 2) marked reduction in all classes of serum immunoglobulins,
and 3) absent B cells (CD19+ cells). The decrease in numbers of peripheral B cells is a key feature,
though this also can be seen in a small subset of patients with common variable immunodeficiency
(CVID). As well, some BTK variants can preserve small numbers of circulating B cells and, therefore,
all the 3 criteria mentioned above need to be evaluated. Patients should be assessed for the presence
of Btk protein by flow cytometry, although normal results by flow cytometry do not rule out the presence
of a BTK variant with aberrant protein function (despite normal protein expression). The diagnosis is
established or confirmed only in those individuals who have a variant identified in the BTK gene by
gene sequencing or who have male family members with hypogammaglobulinemia with absent or low
B cells. Appropriate clinical history is required with or without abnormal Btk protein results by flow
cytometry. It was shown that there are XLA patients with mothers who have normal Btk protein
expression by flow cytometry and normal BTK genotyping and that the variant in the patient is a result
of de novo variants in the maternal germline. In the same study, it was shown that there can be female
carriers who have normal Btk protein expression but are genetically heterozygous and they do not show
abnormal protein expression due to extreme skewed inactivation of the mutant X-chromosome.(6) Also,
the presence of 1 copy of the normal BTK gene and associated normal Btk protein can stabilize mutant
protein abrogating the typical bimodal pattern of protein expression seen in female carriers. Therefore,
female carrier status can only conclusively be determined by genetic testing, especially if the Btk
protein flow test is normal. It is important to keep in mind that the mere presence of BTK gene variants
does not necessarily correlate with a diagnosis of XLA unless the appropriate clinical and
immunological features are present.(9,10)
Useful For: Preferred test for confirming a diagnosis of X-linked agammaglobulinemia (XLA) in males with a history of recurrent sinopulmonary infections, profound hypogammaglobulinemia, and below 1% peripheral B cells. In females, this is the most useful test for identifying carriers of XLA. By including protein and gene analysis, this test provides a comprehensive assessment and enables appropriate genotype-phenotype correlations.

Interpretation: A patient-specific interpretive report is provided.

Reference Values:
BTKSP: An interpretive report will be provided.

BTK: Bruton tyrosine kinase (Btk) expression will be reported as present, absent, partial deficiency, or mosaic (carrier).

Clinical References:

**BTKMP**

Bruton Tyrosine Kinase (BTK) Genotype and Protein Analysis, Known Mutation Sequencing and Flow Cytometry

Clinical Information: X-linked agammaglobulinemia (XLA) is a humoral primary immunodeficiency affecting males in approximately 1 in 200,000 live births. XLA is caused by variants in the Bruton tyrosine kinase gene (BTK), which results in a profound block in B-cell development within the bone marrow and a significant reduction, or complete absence, of mature B cells in peripheral blood. Approximately 85% of male patients with defects in early B-cell development have XLA. Due to the lack of mature B cells, XLA patients have markedly reduced levels of all major classes of immunoglobulins in the serum and are, therefore, susceptible to severe and recurrent bacterial infections. Pneumonia, otitis media, enteritis, and recurrent sinopulmonary infections are among the key clinical diagnostic characteristics of the disease. The spectrum of infectious complications also includes enteroviral meningitis, septic arthritis, cellulitis, and empyema, among others. The disease typically manifests in male children younger than 1 year of age. BTK, the only gene associated with XLA, maps to the X-chromosome at Xq21.3-Xq22 and consists of 19 exons spanning 37.5 kb genomic DNA. BTK encodes a nonreceptor tyrosine kinase of the Btk/Tec family. The Bruton tyrosine kinase (Btk) protein consists of 5 structural domains (PH, TH, SH3, SH2, and TK). Variants causing XLA have been found in all domains of the BTK gene, as well as noncoding regions of the gene. Missense variants account for 40% of all variants, while nonsense variants account for 17%, deletions 20%, insertions 7%, and splice-site variants 16%. Over 600 unique variants in the BTK gene have been detected by full gene sequencing and are listed in BTKbase, a database for BTK variants (http://bioinf.uta.fi/BTKbase).
Genotype-phenotype correlations have not been completely defined for BTK, but it is clear that nonsense variants are overrepresented 4-fold compared to substitutions, which indicates that the latter may be tolerated without causing a phenotype. The type and location of the variant in the gene clearly affects the severity of the clinical phenotype. Some variants manifest within the first year or 2 of life, enabling an early diagnosis. Others present with milder phenotypes, resulting in diagnosis later in childhood or in adulthood.(5) Delayed diagnoses can be partly explained by the variable severity of XLA, even within families in which the same variant is present. While the disease is considered fully penetrant, the clinical phenotype can vary considerably depending on the nature of the specific BTK variant.(5) Lyonization of this gene is not typical and only 1 case of XLA in a female has been reported so far due to skewed lyonization in a carrier female. Therefore, females with clinical features that are identical to XLA should be evaluated for autosomal recessive agammaglobulinemia when deemed clinically appropriate(6) and for XLA, if a male parent is affected with the disease. A flow cytometry test for intracellular Btk in monocytes using an anti-Btk monoclonal antibody was developed by Futatani et al, which was used to evaluate both XLA patients and carriers.(7) In this study, 41 unrelated XLA families were studied and deficient Btk protein expression was seen in 40 of these 41 patients, with complete Btk deficiency in 35 patients and partial Btk deficiency in 5 patients. One patient had a normal level of Btk protein expression. The 6 patients with partial or normal Btk expression had missense BTK variants. Additionally, the flow cytometry assay detected carrier status in the mothers of 35 of the 41 patients (approximately 85%). In the 6 patients where the Btk expression was normal in the mothers of XLA patients, it was noted that all these patients were sporadic cases without previous family history of the disease.(7) It appears, therefore, that most BTK variants result in deficient expression of Btk protein, which can be detected by flow cytometry in monocytes.(7,8) Also, the mosaic expression of Btk protein in the monocytes by flow cytometry is potentially useful in the diagnosis of female carriers.(8) The flow cytometry test therefore provides a convenient screening tool for the diagnosis of XLA with confirmation of the diagnosis by BTK genotyping.(7,8) In the rare patient with the clinical features of XLA but normal Btk protein expression, BTK genotyping must be performed to determine the presence of a variant. A diagnosis of XLA should be suspected in males with 1) early-onset bacterial infections, 2) marked reduction in all classes of serum immunoglobulins, and 3) absent B cells (CD19+ cells). The decrease in numbers of peripheral B cells is a key feature, though this also can be seen in a small subset of patients with common variable immunodeficiency (CVID). As well, some BTK variants can preserve small numbers of circulating B cells and, therefore, all the 3 criteria mentioned above need to be evaluated. Patients should be assessed for the presence of Btk protein by flow cytometry, although normal results by flow cytometry do not rule out the presence of a BTK variant with aberrant protein function (despite normal protein expression). The diagnosis is established or confirmed only in those individuals who have a variant identified in the BTK gene by gene sequencing or who have male family members with hypogammaglobulinemia with absent or low B cells. Appropriate clinical history is required with or without abnormal Btk protein results by flow cytometry. It was shown that there are XLA patients with mothers who have normal Btk protein expression by flow cytometry and normal BTK genotyping and that the variant in the patient is a result of de novo variants in the maternal germline. In the same study, it was shown that there can be female carriers who have normal Btk protein expression but are genetically heterozygous, and they do not show abnormal protein expression due to extreme skewed inactivation of the mutant X chromosome.(6) Also, the presence of 1 copy of the normal BTK gene and associated normal Btk protein can stabilize mutant protein abrogating the typical bimodal pattern of protein expression seen in female carriers. Therefore, female carrier status can only conclusively be determined by genetic testing, especially if the Btk protein flow test is normal. It is important to keep in mind that the mere presence of BTK gene variants does not necessarily correlate with a diagnosis of XLA unless the appropriate clinical and immunological features are present.(9,10)

Useful For: Preferred test for confirming a diagnosis of X-linked agammaglobulinemia (XLA) in male family members of affected individuals with known BTK variants Preferred test for determining carrier status of female relatives of male XLA patients with known BTK variants By including protein and gene analysis, this test provides a comprehensive assessment and enables appropriate genotype-phenotype correlations.

Interpretation: A patient-specific interpretive report is provided.

Reference Values:
BTKKM:
An interpretive report will be provided.

**BTK:**

Bruton tyrosine kinase (Btk) expression will be reported as present, absent, partial deficiency, or mosaic (carrier).

**Clinical References:**

BTKS 89307

**Bruton Tyrosine Kinase (BTK) Genotype, Full Gene Sequence, Blood**

**Clinical Information:**
X-linked agammaglobulinemia (XLA) is a humoral primary immunodeficiency affecting males in approximately 1 in 200,000 live births. XLA is caused by variants in the Bruton tyrosine kinase gene (BTK), which results in a profound block in B-cell development within the bone marrow and a significant reduction, or complete absence, of mature B cells in peripheral blood. Approximately 85% of male patients with defects in early B-cell development have XLA. Due to the lack of mature B cells, XLA patients have markedly reduced levels of all major classes of immunoglobulins in the serum and are, therefore, susceptible to severe and recurrent bacterial infections. Pneumonia, otitis media, enteritis, and recurrent sinopulmonary infections are among the key diagnostic clinical characteristics of the disease. The spectrum of infectious complications also includes enteroviral meningitis, septic arthritis, cellulitis, and empyema, among others. The disease typically manifests in male children younger than 1 year. BTK, the only gene associated with XLA, maps to the X chromosome at Xq21.3-Xq22 and consists of 19 exons spanning 37.5 kb genomic DNA. BTK encodes a nonreceptor tyrosine kinase of the Btk/Tec family. The Btk protein consists of 5 structural domains (PH, TH, SH3, SH2, and TK). Variants causing XLA have been found in all domains of the BTK gene, as well as noncoding regions of the gene. Over 800 unique variants in BTK have been detected by full gene sequencing and are listed in BTKbase, a database for BTK variants (http://structure.bmc.lu.se/idbase/BTKbase/). Missense variants account for approximately 33% of unique variants, nonsense variants 13%, frameshift 25%, in-frame deletions and insertions 4%, large deletions 3% to 5%, and intronic and complex variants make up the remainder. Patients with a large deletion spanning the BTK gene may also impact the adjacent TIMM8A gene (also known as DDP) resulting in both XLA and deafness-dystonia-optic neuropathy syndrome (DDS or Mohr-Tranebjærg syndrome). Genotype-phenotype correlations have not been completely defined for BTK, but it is clear that nonsense and frameshift variants are overrepresented 4-fold compared with substitutions, which indicates that the latter may be tolerated without causing a phenotype or with a milder phenotype or later age at presentation. Some individuals present within the first 2 years of life, enabling an early diagnosis. Others present with milder phenotypes, resulting in diagnosis later in childhood or in
adulthood. Delayed diagnoses can be partly explained by the variable severity of XLA, even within families in which the same variant is present. While the disease is considered fully penetrant, the clinical phenotype can vary considerably depending on the nature of the specific BTK variant. Lyonization of this gene is not typical and only 1 case of XLA in a female has been reported so far due to skewed lyonization in a carrier female. Therefore, females with clinical features that are identical to XLA should be evaluated for autosomal recessive agammaglobulinemia when deemed clinically appropriate and for XLA, if a male parent is affected with the disease. A diagnosis of XLA should be suspected in males with 1) early-onset bacterial infections, 2) marked reduction in all classes of serum immunoglobulins, and 3) absent B cells (CD19+ cells). The decrease in numbers of peripheral B cells is a key feature, though this also can be seen in a small subset of patients with common variable immunodeficiency (CVID). Conversely, some BTK variants can preserve small numbers of circulating B cells and, therefore, all 3 of the criteria mentioned above need to be evaluated. The preferred approach for confirming a diagnosis of XLA in males and identifying carrier females requires testing for the Btk protein expression on B cells by flow cytometry and genetic testing for a BTK variant. Patients can be screened for the presence of Btk protein by flow cytometry (BTK / Bruton Tyrosine Kinase [Btk], Protein Expression, Flow Cytometry, Blood); however, normal results by flow cytometry do not rule out the presence of a BTK variant with normal protein expression but aberrant protein function. The diagnosis is confirmed only in those individuals with appropriate clinical history who have a variant identified within BTK by gene sequencing or who have male family members with hypogammaglobulinemia with absent or low B cells.

**Useful For:** Confirming a diagnosis of X-linked agammaglobulinemia (XLA) in male patients with a history of recurrent sinopulmonary infections, profound hypogammaglobulinemia, and less than 1% peripheral B cells, with or without abnormal Bruton tyrosine kinase (Btk) protein expression by flow cytometry Evaluating for the presence of BTK variants in female relatives (of male XLA patients) who do not demonstrate carrier phenotype by Btk flow cytometry

**Interpretation:** A patient-specific interpretive report is provided.

**Reference Values:**

An interpretive report will be provided.

**Clinical References:**


**BTKK**

**Bruton Tyrosine Kinase (BTK) Genotype, Known Mutation, Blood**

**Clinical Information:** X-linked agammaglobulinemia (XLA) is a humoral primary immunodeficiency affecting males in approximately 1 in 200,000 live births. XLA is caused by variants in the Bruton tyrosine kinase gene (BTK), which results in a profound block in B-cell development within the bone marrow and a significant reduction, or complete absence, of mature B cells in peripheral blood. Approximately 85% of male patients with defects in early B-cell development have XLA. Due to the lack of mature B cells, XLA patients have markedly reduced levels of all major classes of immunoglobulins in the serum and are, therefore, susceptible to severe and recurrent bacterial infections. Pneumonia, otitis media, enteritis, and recurrent sinopulmonary infections are among the key diagnostic clinical characteristics of the disease. The spectrum of infectious complications also includes enteroviral
meningitis, septic arthritis, cellulitis, and empyema, among others. The disease typically manifests in male children younger than 1 year. BTK, the only gene associated with XLA, maps to the X chromosome at Xq21.3-Xq22 and consists of 19 exons spanning 37.5 kb genomic DNA.(4) BTK encodes a nonreceptor tyrosine kinase of the Btk/Tec family. The Btk protein consists of 5 structural domains (PH, TH, SH3, SH2, and TK). Variants causing XLA have been found in all domains of the BTK gene, as well as noncoding regions of the gene. Over 800 unique variants in BTK have been detected by full gene sequencing and are listed in BTKbase, a database for BTK variants (http://structure.bmc.lu.se/idbase/BTKbase/).(5) Missense variants account for approximately 33% of unique variants, nonsense variants 13%, frameshift 25%, in-frame deletions and insertions 4%, large deletions 3% to 5%, and intronic and complex variants make up the remainder. With patients with a large deletion spanning the BTK gene may also impact the adjacent TIMM8A gene (also known as DDP) resulting in both XLA and deafness-dystonia-optic neuropathy syndrome (DDS or Mohr-Tranebjærg syndrome). Genotype-phenotype correlations have not been completely defined for BTK, but it is clear that nonsense and frameshift variants are overrepresented 4-fold compared with substitutions, which indicates that the latter may be tolerated without causing a phenotype or with a milder phenotype or later age at presentation. Some individuals present within the first 2 years of life, enabling an early diagnosis. Others present with milder phenotypes, resulting in diagnosis later in childhood or in adulthood.(5) Delayed diagnoses can be partly explained by the variable severity of XLA, even within families in which the same variant is present. While the disease is considered fully penetrant, the clinical phenotype can vary considerably depending on the nature of the specific BTK variant.(5) Lyonization of this gene is not typical and only 1 case of XLA in a female has been reported so far due to skewed lyonization in a carrier female. Therefore, females with clinical features that are identical to XLA should be evaluated for autosomal recessive agammaglobulinemia when deemed clinically appropriate(6) and for XLA, if a male parent is affected with the disease. Diagnosis of XLA should be suspected in males with 1) early-onset bacterial infections, 2) marked reduction in all classes of serum immunoglobulins, and 3) absent B cells (CD19+ cells). The decrease in numbers of peripheral B cells is a key feature, though this also can be seen in a small subset of patients with common variable immunodeficiency (CVID). Conversely, some BTK variants can preserve small numbers of circulating B cells and, therefore, all 3 of the criteria mentioned above need to be evaluated. The preferred approach for confirming a diagnosis of XLA in males and identifying carrier females requires testing for the Btk protein expression on B cells by flow cytometry and genetic testing for a BTK variant. Patients can be screened for the presence of Btk protein by flow cytometry (BTK / Bruton Tyrosine Kinase [Btk], Protein Expression, Flow Cytometry, Blood); however, normal results by flow cytometry do not rule out the presence of a BTK variant with normal protein expression but aberrant protein function. The diagnosis is confirmed only in those individuals with appropriate clinical history who have a variant identified within BTK by gene sequencing or who have other male family members with hypogammaglobulinemia with absent or low B cells.

**Useful For:** As a follow-up confirmatory genetic test for relatives of X-linked agammaglobulinemia (XLA) patients with a previously identified Bruton tyrosine kinase gene (BTK) variant, after abnormal Btk protein expression has been previously demonstrated (eg, BTK / Bruton Tyrosine Kinase [Btk], Protein Expression, Flow Cytometry, Blood)

**Interpretation:** A patient-specific interpretive report is provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
**Bruton Tyrosine Kinase (Btk), Protein Expression, Flow Cytometry, Blood**

**Clinical Information:** The differential diagnosis for patients with primary hypogammaglobulinemia of unclear etiology (after other secondary causes of hypogammaglobulinemia have been ruled out) includes common variable immunodeficiency (CVID) and X-linked agammaglobulinemia (XLA). CVID is the most common diagnosis of humoral immunodeficiency, particularly in adults, but also in children over 4 years of age. However, adult male patients with XLA may be misdiagnosed with CVID. XLA is an independent humoral immunodeficiency and should not be regarded as a subset of CVID. The BTK gene is present on the long arm of the X-chromosome and encodes for a cytoplasmic tyrosine kinase with 5 distinct structural domains. While BTK gene sequencing is the gold standard for definitively identifying mutations and confirming a diagnosis of XLA, it is labor intensive and expensive. Flow cytometry is a screening test for XLA and should be included in the evaluation of patients with possible CVID, particularly in male patients with less than 1% B cells. Bruton tyrosine kinase (Btk) is an intracellular protein and absence of the Btk protein by flow cytometry provides a strong rationale for performing a BTK gene-sequencing test. However, 20% to 30% of XLA patients may have intact or truncated Btk protein with abnormal function; therefore, genetic analysis remains the more definitive test for diagnosing XLA (besides other clinical and immunological parameters). XLA is a prototypical humoral immunodeficiency caused by mutations in the BTK gene, which encodes Btk, a hematopoietic-specific tyrosine kinase. XLA is characterized by normal, reduced, or absent Btk expression in monocytes and platelets, a significant reduction or absence of circulating B cells in blood, and profound hypogammaglobulinemia of all isotypes (IgG, IgA, IgM, and IgE). The clinical presentation includes early onset of recurrent bacterial infections, and absent lymph nodes and tonsils. Btk plays a critical role in B-cell differentiation. The defect in Btk may be "leaky" in some patients (ie, a consequence of mutations in the gene that result in a milder clinical and laboratory phenotype), such that these patients may have some levels of IgG and/or IgM and a small number of B cells in blood.(1) The vast majority of XLA patients are diagnosed in childhood (median age of diagnosis in patients with sporadic XLA is 26 months), although some patients are recognized in early adulthood or later in life. The diagnosis of XLA in both children and adults indicates that the disorder demonstrates considerable clinical phenotypic heterogeneity, depending on the position of the mutations within the gene. Females are typically carriers and asymptomatic. Testing in adult females should be limited to those in their child-bearing years (<45 years). Carrier testing ideally should be confirmed by genetic testing since it is possible to have a normal flow cytometry test for protein expression in the presence of heterozygous (carrier) BTK gene mutations. Flow cytometry is a preliminary screening test for XLA. It is important to keep in mind that this flow cytometry test is only a screening tool and approximately 20% to 30% of patients who have a mutation within the BTK gene have normal protein expression (again related to the position of the mutation in the gene and the antibody used for flow cytometric analysis). Therefore, in addition to clinical correlation, genetic testing is recommended to confirm a diagnosis of XLA. Furthermore, it is helpful to correlate gene and protein data with clinical history (genotype-phenotype correlation) in making a final diagnosis of XLA. Consequently, the preferred test for XLA is BTKFP / Bruton Tyrosine Kinase (BTK) Genotype and Protein Analysis, Full Gene Sequence and Flow Cytometry, which includes both flow cytometry and gene sequencing to confirm the presence of a BTK mutation. If a familial mutation has already been identified, then BTKMP / Bruton Tyrosine Kinase (BTK) Genotype and Protein Analysis, Known Mutation Sequencing and Flow Cytometry should be ordered.

**Useful For:** Preliminary screening for X-linked agammaglobulinemia (XLA), primarily in male patients (<65 years of age) or female carriers (child-bearing age: <45 years) Because genotype-phenotype correlations are important, the preferred test for confirming a diagnosis of XLA in males and identifying carrier females is: -BTKFP / Bruton Tyrosine Kinase (BTK) Genotype and Protein Analysis, Full Gene Sequence and Flow Cytometry -In families where a BTK mutation has already been identified, order BTKMP / Bruton Tyrosine Kinase (BTK) Genotype and Protein Analysis, Known Mutation Sequencing and Flow Cytometry

**Interpretation:** Results are reported as Bruton tyrosine kinase (Btk) protein expression present (normal) or absent (abnormal) in monocytes. Additionally, mosaic Btk expression (indicative of a carrier)
and reduced Btk expression (consistent with partial Btk protein deficiency) are reported when present and correlated with a healthy experimental control. BTK genotyping (BTKS / Bruton Tyrosine Kinase (BTK) Genotype, Full Gene Sequence or BTKK / Bruton Tyrosine Kinase (BTK) Genotype, Known Mutation) should be performed in the following situations: -To confirm any abnormal flow cytometry result -In the rare patient with the clinical features of X-linked agammaglobulinemia (XLA), but normal Btk protein expression -In mothers of patients who do not show the classic carrier pattern of bimodal protein expression (to determine if there is maternal germinal mosaicism or skewed mutant X-chromosome inactivation) or there is dominant expression of the normal protein in the presence of 1 copy of a mutation.

Reference Values:

Present: Bruton tyrosine kinase (Btk) expression will be reported as present, absent, partial deficiency, or mosaic (carrier).


Buckwheat, IgE
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venen allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<th>Class IgE kU/L</th>
<th>Interpretation</th>
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<tr>
<td>1</td>
<td>0.35-0.69</td>
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<tr>
<td>2</td>
<td>0.70-3.49</td>
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Budgerigar Droppings, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<th>IgE kU/L</th>
<th>Interpretation</th>
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</tr>
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<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>4</td>
<td>50.0-99.9</td>
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</tr>
<tr>
<td>5</td>
<td>&gt; or =100</td>
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</tbody>
</table>

Reference values apply to all ages.

**Budgerigar Feathers, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>0</td>
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<tr>
<td>1</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>


**Bullous Pemphigoid, BP180 and BP230, IgG Antibodies, Serum**

**Clinical Information:** Bullous pemphigoid (BP) is chronic pruritic blistering disorder found mainly in aged persons, characterized by the development of tense blisters over an erythematous or urticarial base. IgG antibasement membrane zone antibodies are found in the serum of patients, and linear IgG and C3 sediment is found on the basement membrane zone of the lesion. Several well characterized variants exist including localized, mucous membrane predominant and pemphigoid gestationis, also referred to as herpes gestationis. Target antigens of the autoantibodies in BP patient serum are BP230 and BP180 also called BPAG1 and BPAG2. Molecular weight of these antigens is 230 kD and 180 kD, respectively. BP180 is thought to be the direct target of the autoantibody because of its location along the basement membranes, and the autoantibody against BP230 is thought to be secondarily produced.
Useful For: Bullous pemphigoid (BP) BP180 and BP230 enzyme-linked immunosorbent assay are sensitive, objective, and specific tests that should be considered as an initial screening test in the diagnosis of pemphigoid and its variants. To compare these results with the standard serum test of indirect immunofluorescence utilizing monkey esophagus substrate.

Interpretation: Antibodies to bullous pemphigoid (BP) BP180 and BP230 have been shown to be present in most patients with pemphigoid. Adequate sensitivities and specificity for disease are documented and Mayo’s experience demonstrates a very good correlation between BP180 and BP230 results and the presence of pemphigoid (see Supportive Data). However, in those patients strongly suspected to have pemphigoid, either by clinical findings or by routine biopsy, and in whom the BP180/BP230 assay is negative, follow-up testing by CIFS / Cutaneous Immunofluorescence Antibodies (IgG), Serum is recommended. Antibody titer correlates with disease activity in many patients. Patients with severe disease can usually be expected to have high titers of antibodies to BP. Titters are expected to decrease with clinical improvement.

Reference Values:
BP180
<9.0 U (negative)
> or =9.0 U (positive)

BP230
<9.0 U (negative)
> or =9.0 U (positive)

of the potency of its parent. The glucuronide metabolites are inactive.(1) The primary clinical utility of quantification of buprenorphine in urine is to identify patients that have strayed from opioid dependence therapy.

**Useful For:** Monitoring of compliance of buprenorphine therapy Detection and confirmation of the illicit use of buprenorphine

**Interpretation:** The presence of buprenorphine above 5.0 ng/mL or norbuprenorphine above 2.5 ng/mL is a strong indicator that the patient has used buprenorphine.

**Reference Values:**
Negative

Cutoff concentrations:
- Buprenorphine: 5.0 ng/mL
- Norbuprenorphine: 2.5 ng/mL

**Clinical References:**

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**BUPM 66200**

**Buprenorphine and Norbuprenorphine, Random, Urine**

**Clinical Information:** Clinically, buprenorphine is utilized as a substitution therapy for opioid dependence and as an analgesic. Buprenorphine is a partial agonist of the mu-opioid receptor. These mu binding sites are discretely distributed in the human brain, spinal cord, and other tissue. The clinical effects of mu receptor agonists are sedation, euphoria, respiratory depression, and analgesia. As a partial mu receptor agonist, buprenorphine's clinical effects are decreased, giving buprenorphine a wider safety margin.(1) Buprenorphine has a prolonged duration of activity. The combination of decreased clinical effects and prolonged activity gives buprenorphine the added advantage of a delayed and decreased withdrawal syndrome, compared to other opioids.(1) Compared to morphine, buprenorphine is 25 to 40 times more potent.(1) As with any opioid, abuse is always a concern. To reduce illicit use of buprenorphine, it is available mixed with naloxone in a ratio of 4:1. When the combination is taken as prescribed, only small amounts of naloxone will be absorbed. However, if the combination is transformed into the injectable form, naloxone then acts as an opioid receptor antagonist.

Buprenorphine is metabolized through N-dealkylation to norbuprenorphine through cytochrome P450 3A4. Both parent and metabolite then undergo glucuronidation. Norbuprenorphine is an active metabolite possessing one-fifth of the potency of its parent. The glucuronide metabolites are inactive.(1) The primary clinical utility of quantification of buprenorphine in urine is to identify patients that have strayed from opioid dependence therapy.

**Useful For:** Monitoring of compliance utilizing buprenorphine Detection and confirmation of the illicit use of buprenorphine

**Interpretation:** The presence of buprenorphine above 5.0 ng/mL or norbuprenorphine above 2.5 ng/mL is a strong indicator that the patient has used buprenorphine.

**Reference Values:**
Negative

Cutoff concentrations:
- Buprenorphine: 5.0 ng/mL
Norbuprenorphine: 2.5 ng/mL


**Buprenorphine Screen with Reflex, Urine**

**Clinical Information:** Clinically, buprenorphine is utilized as a substitution therapy for opioid dependence and as an analgesic. Buprenorphine is a partial agonist of the mu-opioid receptor. These mu binding sites are discretely distributed in the human brain, spinal cord, and other tissue. The clinical effects of mu receptor agonists are sedation, euphoria, respiratory depression, and analgesia. As a partial mu receptor agonist, buprenorphine's clinical effects are decreased, giving buprenorphine a wider safety margin. Buprenorphine has a prolonged duration of activity. The combination of decreased clinical effects and prolonged activity gives buprenorphine the added advantage of a delayed and decreased withdrawal syndrome, compared to other opioids. Compared to morphine, buprenorphine is 25 to 40 times more potent. As with any opioid, abuse is always a concern. To reduce illicit use of buprenorphine, it is available mixed with naloxone in a ratio of 4:1. When the combination is taken as prescribed, only small amounts of naloxone will be absorbed. However, if the combination is transformed into the injectable form, naloxone then acts as an opioid receptor antagonist. Buprenorphine is metabolized through N-dealkylation to norbuprenorphine through cytochrome P450 3A4. Both parent and metabolite then undergo glucuronidation. Norbuprenorphine is an active metabolite possessing one fifth of the potency of its parent. The glucuronide metabolites are inactive. This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also can have a false-negative due to the antibody's ability to cross-react with different drugs in the target class.

**Useful For:** Screening for drug abuse or use of buprenorphine

**Interpretation:** This assay only provides a preliminary analytical test result. A more specific alternative method (ie, liquid chromatography-tandem mass spectrometry: LC-MS/MS) must be used to obtain a confirmed analytical result.

**Reference Values:**

<p>| |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Screening cutoff concentration:</td>
</tr>
<tr>
<td>Buprenorphine: 5 ng/mL.</td>
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**Buprenorphine Screen, Urine**

**Clinical Information:** Clinically, buprenorphine is utilized as a substitution therapy for opioid dependence and as an analgesic. Buprenorphine is a partial agonist of the mu-opioid receptor. These mu binding sites are discretely distributed in the human brain, spinal cord, and other tissue. The clinical effects of mu receptor agonists are sedation, euphoria, respiratory depression, and analgesia. As a partial mu receptor agonist, buprenorphine's clinical effects are decreased, giving buprenorphine a wider safety margin.
Buprenorphine has a prolonged duration of activity. The combination of decreased clinical effects and prolonged activity gives buprenorphine the added advantage of a delayed and decreased withdrawal syndrome, compared to other opioids. Compared to morphine, buprenorphine is 25 to 40 times more potent. As with any opioid, abuse is always a concern. To reduce illicit use of buprenorphine, it is available mixed with naloxone in a ratio of 4:1. When the combination is taken as prescribed, only small amounts of naloxone will be absorbed. However, if the combination is transformed into the injectable form, naloxone then acts as an opioid receptor antagonist. Buprenorphine is metabolized through N-dealkylation to norbuprenorphine through cytochrome P450 3A4. Both parent and metabolite then undergo glucuronidation. Norbuprenorphine is an active metabolite possessing one fifth of the potency of its parent. The glucuronide metabolites are inactive. This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also can have a false-negative due to the antibody’s ability to cross-react with different drugs in the target class.

**Useful For:** Screening for drug abuse or use of buprenorphine

**Interpretation:** This assay only provides a preliminary analytical test result. A more specific alternative method (ie, liquid chromatography-tandem mass spectrometry: LC-MS/MS) must be used to obtain a confirmed analytical result.

**Reference Values:**
- Negative
- Screening cutoff concentration:
  - Buprenorphine: 5 ng/mL

**Clinical References:**

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### FBUPS 75260 Bupropion and Metabolite, Serum/Plasma

**Interpretation:** Bupropion: Maximum antidepressant response was observed at trough plasma concentrations of 50 – 100 ng/mL bupropion with virtually no response below 25 ng/mL. Reported average bupropion peak plasma concentrations: Adults: Single 100 mg IR – 120 +/- 10 ng/mL (Males): 150 +/- 10 ng/mL (Females) Adults: Single 200 mg IR -220 +/- 20 ng/mL (Males): 270 +/- 20 ng/mL (Females) Adults: Single 150 mg SR – 140 +/- 20 ng/mL Juveniles: 100 mg/day SR for 2 weeks – 25 +/- 8 ng/mL Juveniles: 200 mg/day SR for 2 weeks – 53 +/- 22 ng/mL Specimens must be kept frozen. If specimens are not kept frozen, this may cause lower or negative values. Hydroxybupropion: 8 adults (Age 22 – 42) taking thrice daily 100 mg normal release bupropion for 2 weeks had an average peak plasma concentration of 1000 +/- 70 ng/mL hydroxybupropion. Juvenile patients take once daily, extended release bupropion for two weeks had the following peak plasma concentrations: 100 mg/day (n = 11), 450 +/- 210 ng/mL hydroxybupropion 200 mg/day (n = 8), 710 +/- 350 ng/mL hydroxybupropion

**Reference Values:**
- Reporting Limit:
  - Bupropion: 5.0 ng/mL
  - Hydroxybupropion: 50 ng/mL

### FBUS 91115 Buspirone (Buspar)

**Reference Values:**
- Units: ng/mL

Therapeutic and toxic ranges have not been established.
Expected serum buspirone concentrations in patients taking recommended daily dosages: up to 10.00 ng/mL.

**Busulfan, Intravenous Dose, Area Under the Curve (AUC), Plasma**

**Clinical Information:** Busulfan is an alkylating agent used to ablate bone marrow cells prior to hematopoietic stem cell transplantation for chronic myelogenous leukemia.(1) Busulfan is typically administered intravenously (IV) at the recommended dosage of 0.8 mg/kg of actual or ideal body weight (whichever is lower) and given once every 6 hours over 4 days for a total of 16 doses. Dose-limiting toxicity of busulfan includes veno-occlusive liver disease, seizures, and coma. To avoid toxicity while ensuring busulfan dose adequacy to completely ablate the bone marrow, IV dosing should be guided by pharmacokinetic (PK) evaluation of area under the curve (AUC) and clearance after the first dose.(2) The PK evaluation should be carried out at the end of the first dose, with results of PK testing available to facilitate dose adjustment before beginning the fifth dose.

**Useful For:** Guiding dosage adjustments to achieve complete bone marrow ablation while minimizing dose-dependent toxicity

**Interpretation:** This test should only be ordered when the following criteria are met: - Busulfan dosing protocol must be intravenous (IV) administration of 0.8 mg/kg doses every 6 hours over 4 days, for a total of 16 doses - Specimens must be drawn as described below: - 1 specimen drawn immediately after termination of a 2-hour IV infusion of busulfan - 1 specimen drawn 1 hour after the infusion is terminated - 1 specimen drawn 2 hours after the infusion is terminated - 1 specimen drawn 4 hours after the infusion is terminated These results will be used to calculate a 6-hour area under the curve (AUC). If a different dosing or specimen collection protocol is used, or if different calculations are required, contact the Laboratory Director. The optimal result for AUC (6 hour) derived from this pharmacokinetic (PK) evaluation of IV busulfan is 1,100 (mcmol/L)(min). AUC results greater than 1,500 (mcmol/L)(min) are associated with hepatic veno-occlusive disease. A dose reduction should be considered before the next busulfan infusion. AUC results below 900 (mcmol/L)(min) are consistent with incomplete bone marrow ablation. A dose increase should be considered before the next busulfan infusion. Clearance of busulfan in patients with normal renal function is usually in the range of 2.1 to 3.5 (mL/min)/kg. Elevated AUC is typically associated with clearance below 2.5 (mL/min)/kg, most frequently due to diminished activity of glutathione S-transferase A1-1 activity.(3)

**Reference Values:**
- AREA UNDER THE CURVE
  - 900-1,500 (mcmol/L)(min)
- CLEARANCE
  - 2.1-3.5 (mL/minute)/kg


**Butalbital, Serum**

**Clinical Information:** Butalbital is a short-acting barbiturate with hypnotic properties that is used in combination with other drugs such as acetaminophen, salicylate, caffeine, and codeine.(1) Butalbital is administered orally. The duration of its hypnotic effect is about 3 to 4 hours. The drug distributes...
throughout the body, with a volume of distribution (Vd) of 0.8 L/kg, and about 26% of a dose is bound to plasma proteins. Butalbital's half-life is about 35 to 88 hours. Excretion occurs mainly in the urine.(1,2)

**Useful For:** Monitoring butalbital therapy

**Interpretation:** Butalbital concentrations of 10 mcg/mL or greater have been associated with toxicity.

**Reference Values:**
<10 mcg/mL


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**C-Peptide, Serum**

**Clinical Information:** C-peptide (connecting peptide), a 31-amino-acid polypeptide, represents the midportion of the proinsulin molecule. Proinsulin resembles a hairpin structure, with the N-terminal and C-terminal, which correspond to the A and B chains of the mature insulin molecule, oriented parallel to each other and linked by disulfide bonds. The looped portion of the hairpin between the A and B chains is called C-peptide. During insulin secretion it is enzymatically cleaved off and cosecreted in equimolar proportion with mature insulin molecules. Following secretion, insulin and C-peptide enter the portal circulation and are routed through the liver, where at least 50% of the insulin binds to receptors, initiates specific hepatic actions (stimulation of hepatic glucose uptake and suppression of glyconeogenesis, gluconeogenesis, and ketogenesis) and is subsequently degraded. Most of the insulin molecules that pass through the liver into the main circulation bind to peripheral insulin receptors, promoting glucose uptake, while the remaining molecules undergo renal elimination. Unlike insulin, C-peptide is subject to neither hepatic nor significant peripheral degradation, but is mainly removed by the kidneys. As a result, C-peptide has a longer half-life than insulin (30-35 minutes versus 5-10 minutes) and the molar ratio of circulating insulin to circulating C-peptide is generally <1, despite equimolar secretion. Until recently, C-peptide was thought to have no physiological function, but it now appears that there may be specific C-peptide cell-surface receptors (most likely belonging to the super-family of G-protein coupled receptors), which influence endothelial responsiveness and skeletal and renal blood flow. In most disease conditions associated with abnormal serum insulin levels, the changes in serum C-peptide levels parallel insulin-related alterations (insulin to C-peptide molar ratio < or =1). Both serum C-peptide and serum insulin levels are elevated in renal failure and in disease states that lead to augmented primary endogenous insulin secretion (eg, insulinoma, sulfonylurea intoxication). Both also may be raised in any disease states that cause secondary increases in endogenous insulin secretion mediated through insulin resistance, primarily obesity, glucose intolerance, and early type 2 diabetes mellitus (DM), as well as endocrine disorders associated with hypersecretion of insulin-antagonistic hormones (eg, Cushing syndrome, acromegaly). Failing insulin secretion in type 1 DM and longstanding type 2 DM is associated with corresponding reductions in serum C-peptide levels. Discordant serum insulin and serum C-peptide abnormalities are mainly observed in 2 situations: exogenous insulin administration and in the presence of anti-insulin autoantibodies. Factitious hypoglycemia due to surreptitious insulin administration results in inappropriate suppression of endogenous insulin and C-peptide secretion. At the same time, the peripherally administered insulin bypasses the hepatic first-pass metabolism. In these situations, insulin levels are elevated and C-peptide levels are decreased. In patients with insulin antibodies, insulin levels are increased because of the prolonged half-life of autoantibody-bound insulin. Some patients with anti-idiotypic anti-insulin autoantibodies experience episodic hypoglycemia caused by displacement of autoantibody-bound insulin.

**Useful For:** Diagnostic workup of hypoglycemia: -Diagnosis of factitious hypoglycemia due to surreptitious administration of insulin -Evaluation of possible insulinoma -Surrogate measure for the absence or presence of physiological suppressibility of endogenous insulin secretion during diagnostic insulin-induced hypoglycemia (C-peptide suppression test) Assessing insulin secretory reserve in selected diabetic patients (as listed below) who either have insulin autoantibodies or who are receiving
insulin therapy: -Assessing residual endogenous insulin secretory reserve -Monitoring pancreatic and islet cell transplant function -Monitoring immunomodulatory therapy aimed at slowing progression of preclinical, or very early stage type 1 diabetes mellitus

**Interpretation:**
To compare insulin and C-peptide concentrations (ie, insulin to C-peptide ratio):
- Convert insulin to pmol/L: insulin concentration in mcIU/mL x 6.945 = insulin concentration in pmol/L
- Convert C-peptide to pmol/L: C-peptide concentration in ng/mL x 331 = C-peptide concentration in pmol/L

Factitious hypoglycemia due to surreptitious insulin administration results in elevated serum insulin levels and low or undetectable C-peptide levels, with a clear reversal of the physiological molar insulin to C-peptide ratio (< or =1) to an insulin to C-peptide ratio of greater than 1. By contrast, insulin and C-peptide levels are both elevated in insulinoma and the insulin to C-peptide molar ratio is 1 or less.

Sulfonylurea ingestion also is associated with preservation of the insulin to C-peptide molar ratio of 1 or less. In patients with insulin autoantibodies, the insulin to C-peptide ratio may be reversed to greater than 1, because of the prolonged half-life of autoantibody-bound insulin. Dynamic testing may be necessary in the workup of hypoglycemia; the C-peptide suppression test is most commonly employed. C-peptide levels are measured following induction of hypoglycemia through exogenous insulin administration. The test relies on the demonstration of the lack of suppression of serum C-peptide levels within 2 hours following insulin-induced hypoglycemia in patients with insulinoma. Reference intervals have not been formally verified in-house for pediatric patients. The published literature indicates that reference intervals for adult and pediatric patients are comparable.

**Reference Values:**
1.1-4.4 ng/mL

Reference intervals have not been formally verified in-house for pediatric patients. The published literature indicates that reference intervals for adult and pediatric patients are comparable.

**Clinical References:**

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**C-Reactive Protein (CRP) Immunostain, Technical Component Only**

**Clinical Information:**
C-reactive protein (CRP) is an acute-phase reactant associated with host defense that promotes agglutination and complement fixation. CRP can be used with a panel of immunohistochemical markers (beta-catenin, liver fatty acid-binding protein, glutamine synthetase, and amyloid A) to distinguish hepatic adenoma from focal nodular hyperplasia and nonneoplastic liver. CRP, along with amyloid A, is markedly overexpressed in inflammatory (type 3) hepatic adenoma and does not display strong staining in normal liver or in other adenoma types.

**Useful For:**
Classification of hepatic adenomas

**Interpretation:**
This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

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**C-Reactive Protein (CRP), Serum**

**Clinical Information:** C-reactive protein (CRP) is one of the most sensitive acute-phase reactants for inflammation. CRP is synthesized by the liver and consists of 5 identical polypeptide chains that form a 5-membered ring with a molecular weight of 105,000 daltons. Complexed CRP activates the classical complement pathway. The CRP response frequently precedes clinical symptoms, including fever. CRP elevations are nonspecific and may be useful for the detection of systemic inflammatory processes; to assess treatment of bacterial infections with antibiotics; to detect intrauterine infections with concomitant premature amniorrhexis; to differentiate between active and inactive forms of disease with concurrent infection, eg, in patients suffering from systemic lupus erythematosus or colitis ulcerosa; to therapeutically monitor rheumatic disease and assess anti-inflammatory therapy; to determine the presence of postoperative complications at an early stage, such as infected wounds, thrombosis, and pneumonia; and to distinguish between infection and bone marrow rejection. Postoperative monitoring of CRP levels of patients can aid in the recognition of unexpected complications (persisting high or increasing levels). Measuring changes in the concentration of CRP provides useful diagnostic information about the level of acuity and severity of a disease. It also allows judgments about the disease genesis. Persistence of a high serum CRP concentration is usually a grave prognostic sign that generally indicates the presence of an uncontrolled infection.

**Useful For:** Detecting systemic inflammatory processes Detecting infection and assessing response to antibiotic treatment of bacterial infections Differentiating between active and inactive disease forms with concurrent infection

**Interpretation:** In normal healthy individuals, C-reactive protein (CRP) is a trace protein (<8 mg/L). Elevated values are consistent with an acute inflammatory process. After onset of an acute phase response, the serum CRP concentration rises rapidly (within 6-12 hours and peaks at 24-48 hours) and extensively. Concentrations above 100 mg/L are associated with severe stimuli such as major trauma and severe infection (sepsis).

**Reference Values:**
< or =8.0 mg/L

**Clinical References:** Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. Edited by CA Burtis, ER Ashwood, DE Bruns. St. Louis, MO. Elsevier Saunders, 2012

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**C-Reactive Protein, High Sensitivity, Serum**

**Clinical Information:** C-reactive protein (CRP) is a biomarker of inflammation. Plasma CRP concentrations increase rapidly and dramatically (100-fold or more) in response to tissue injury or inflammation. High-sensitivity CRP (hs-CRP) is more precise than standard CRP when measuring baseline (ie, normal) concentrations and enables a measure of chronic inflammation. Atherosclerosis is an inflammatory disease and hs-CRP has been endorsed by multiple guidelines as a biomarker of atherosclerotic cardiovascular disease risk.(1-3) A large prospective clinical trial demonstrated significantly less cardiovascular risk for patients with hs-CRP less than 2.0 mg/L.(1) More aggressive treatment strategies may be warranted in patients with hs-CRP of 2.0 mg/L or higher.

**Useful For:** Assessment of risk of developing myocardial infarction in patients presenting with acute coronary syndromes Assessment of risk of developing cardiovascular disease or ischemic events in individuals who do not manifest disease at present
**Interpretation:** Values greater than 2.0 mg/L suggest an increased likelihood of developing cardiovascular disease or ischemic events.

**Reference Values:**
- Lower risk: <2.0 mg/L
- Higher risk: > or =2.0 mg/L
- Acute inflammation: >10.0 mg/L

**Clinical References:**

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**C1 Esterase (C1ES) Inhibitor Antigen, Serum**

**Clinical Information:** C1 esterase inhibitor blocks the activation of C1 (first component of the complement cascade) to its active form. The deficiency of C1 esterase inhibitor results in the inappropriate activation of C1 and the subsequent release of an activation peptide from C2 with kinin-like activity. This kinin-like peptide enhances vascular permeability. C1 esterase inhibitor deficiency results in hereditary or acquired angioedema. This disease is an autosomal dominant inherited condition, in which exhaustion of the abnormally low levels of C1 esterase inhibitor results in C1 activation, breakdown of C2 and C4, and subsequent acute edema of subcutaneous tissue, the gastrointestinal tract, or the upper respiratory tract. The disease responds to attenuated androgens. Because 15% of C1 inhibitor deficiencies have nonfunctional protein, some patients will have abnormal functional results (FC1EQ / C1 Esterase Inhibitor, Functional Assay, Serum) in the presence of normal (or elevated) antigen levels.

**Useful For:** Diagnosis of hereditary angioedema Monitoring levels of C1 esterase inhibitor in response to therapy

**Interpretation:** Abnormally low results are consistent with a heterozygous C1 esterase inhibitor deficiency and hereditary angioedema. Fifteen percent of hereditary angioedema patients have a normal or elevated level but nonfunctional C1 esterase inhibitor protein. Detection of these patients requires a functional measurement of C1 esterase inhibitor; FC1EQ / C1 Esterase Inhibitor, Functional Assay, Serum. Measurement of C1q antigen levels; C1Q / Complement C1q, Serum, is key to the differential diagnoses of acquired or hereditary angioedema. Those patients with the hereditary form of the disease will have normal levels of C1q, while those with the acquired form of the disease will have low levels. Studies in children show that adult levels of C1 inhibitor are reached by 6 months of age.

**Reference Values:**
19-37 mg/dL

**Clinical References:**
Clinical Information: C1 inhibitor (C1-INH) is a multispecific protease inhibitor that is present in normal human plasma and serum, and which regulates enzymes of the complement, coagulation, fibrinolytic, and kinin-forming systems. The enzymes (proteases) regulated by this protein include the C1r and C1s subunits of the activated first component of complement, activated Hageman factor (factor XIa), kallikrein (Fletcher factor), and plasmin. A deficiency of functionally active C1-INH may lead to life-threatening angioedema. Two major forms of C1-INH deficiency have been reported: the congenital form, termed hereditary angioedema (HAE), and the acquired form that is associated with a variety of diseases, including lymphoid malignancies. HAE is characterized by transient but recurrent attacks of nonpruritic swelling of various tissues throughout the body. The symptomatology depends upon the organs involved. Intestinal attacks lead to a diversity of symptoms including pain, cramps, vomiting, and diarrhea. The most frequent cause of death in this disease is airway obstruction secondary to laryngeal edema occurring during an attack. There are 2 types of HAE that can be distinguished biochemically. Patients with the more common type (85% of HAE patients) have low levels of functional C1-INH and C1-INH antigen. Patients with the second form (15% of HAE patients) have low levels of functional C1-INH but normal or increased levels of C1-INH antigen that is dysfunctional. The variable nature of the symptoms at different time periods during the course of the disease makes it difficult to make a definitive diagnosis based solely on clinical observation.

Useful For: Diagnosing hereditary angioedema and for monitoring response to therapy

Interpretation: Hereditary angioedema (HAE) can be definitely diagnosed by laboratory tests demonstrating a marked reduction in C1 inhibitor (C1-INH) antigen or abnormally low functional C1-INH levels in a patient's plasma or serum that has normal or elevated antigen. Nonfunctional results are consistent with HAE. Patients with current attacks will also have low C2 and C4 levels due to C1 activation and complement consumption. Patients with acquired C1-INH deficiency have a low C1q in addition to low C1-INH.

Reference Values:
>67% normal (normal)
41-67% normal (equivocal)
<41% normal (abnormal)


C1q Complement, Functional, Serum

Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (or mannan binding protein, [MBP]) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex. The first component of complement (C1) is composed of 3 subunits designated as C1q, C1r, and C1s. C1q
recognizes and binds to immunoglobulin complexed to antigen and initiates the complement cascade. Congenital deficiencies of any of the early complement components (C1-C4) result in an inability to generate the peptides that are necessary to clear immune complexes and to attract neutrophils or generate lytic activity. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease and complement deficiency may be an etiologic factor in the development of autoimmune disease. Inherited deficiency of C1 is rare. C1 deficiency is associated with increased incidence of immune complex disease (systemic lupus erythematosus [SLE], polymyositis, glomerulonephritis, and Henoch-Schonlein purpura), and SLE is the most common manifestation of C1 deficiency. The SLE associated with C1 deficiency is similar to SLE without complement deficiency, but the age of onset is often prior to puberty. Low C1 levels have also been reported in patients with abnormal immunoglobulin levels (Bruton's and common variable hypogammaglobulinemia and severe combined immunodeficiency), and this is most likely due to increased catabolism. Complement levels can be detected by antigen assays that quantitate the amount of the protein. For most of the complement proteins a small number of cases have been described in which the protein is present but is non functional. These rare cases require a functional assay to detect the deficiency.

**Useful For:** Diagnosis of first component of complement (C1) deficiency Investigation of a patient with an absent total complement (CH50) level

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or to complement consumption (eg, as a consequence of infectious or autoimmune processes). The measurement of C1q activity is an indicator of the amount of first component of complement (C1) present. Absent C1q levels in the presence of normal C3 and C4 values are consistent with a C1 deficiency. Low C1q levels in the presence of low C4 but normal C3 may indicate the presence of an acquired inhibitor (autoantibody) to C1 esterase inhibitor.

**Reference Values:**
34-63 U/mL

**Clinical References:**

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**C2AG 84141**

**C2 Complement, Antigen, Serum**

**Clinical Information:** Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: (1) the classic pathway (which is activated by immune complexes), (2) the alternative (or properdin) pathway, and (3) the lectin activation (mannan-binding protein, MBP) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). The absence of early components (C1, C2, C4, C3) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to clear immune complexes or to generate lytic activity. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease and complement deficiency may be an etiologic factor in the development of autoimmune disease. Although rare, C2 deficiency is the most common inherited complement deficiency. Homozygous C2 deficiency has an estimated prevalence ranging from 1 in 10,000 to 1 in 40,000 (the prevalence of heterozygotes is 1:100 to 1:50). Half of the homozygous patients...
are clinically normal. However, discoid lupus erythematosus or systemic lupus erythematosus (SLE) occurs in approximately one-third of patients with homozygous C2 deficiency. Patients with SLE and a C2 deficiency frequently have a normal anti-ds DNA titer. Clinically, many have lupus-like skin lesions and photosensitivity, but immunofluorescence studies may fail to demonstrate immunoglobulin or complement along the epidermal-dermal junction. Other diseases reported to be associated with C2 deficiency include dermatomyositis, glomerulonephritis, vasculitis, atrophodema, cold urticaria, inflammatory bowel disease, and recurrent infections.

**Useful For:** Diagnosis of C2 deficiency Investigation of a patient with a low (absent) hemolytic complement (CH50)

**Interpretation:** An inherited complement component deficiency will result in an undetectable complement level. In addition, low or undetectable levels of complement may be due to acquired deficiencies or complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C2 levels in the presence of normal C3 and C4 values are consistent with a C2 deficiency. Low C2 levels in the presence of low C3 and C4 values are consistent with a complement-consumptive process. Low C2 and C4 values in the presence of normal values for C3 is suggestive of C1 esterase inhibitor deficiency. Although there are no pediatric studies on C2, studies on cord blood indicate levels are approximately half adult levels(1) and in other studies(2,3) levels of C1q, C3, and C4 reach adult values by 2 months of age.

**Reference Values:** Only orderable as a reflex. For more information see C2 / C2 Complement, Functional, with Reflex, Serum.

1.1-3.0 mg/dL


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**C2 Complement, Functional, Serum**

**Clinical Information:** The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. This activation process results in the formation of the lytic membrane attack complex, as well as the generation of activation peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The absence of early components (C1, C2, C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to generate lytic activity or to clear immune complexes. Although rare, C2 deficiency is the most common inherited complement deficiency. Homozygous C2 deficiency has an estimated prevalence ranging from 1 in 10,000 to 1 in 40,000 (the prevalence of heterozygotes is 1 in 100 to 1 in 50). Half of the homozygous patients are clinically normal. However, discoid lupus erythematosus or systemic lupus erythematosus (SLE) occurs in approximately one-third of patients with homozygous C2 deficiency. Patients with SLE and a C2 deficiency frequently have a normal anti-ds DNA titer. Clinically, many have lupus-like skin lesions and photosensitivity, but immunofluorescence studies may fail to demonstrate immunoglobulin or complement along the epidermal-dermal junction. Other diseases reported to be associated with C2 deficiency include...
dermatomyositis, glomerulonephritis, vasculitis, atrophodema, cold urticaria, inflammatory bowel disease, and recurrent infections. The laboratory findings that suggest C2 deficiency include a hemolytic complement (CH50) of nearly zero, with normal values for C3 and C4.

**Useful For:** Investigation of a patient with a low (absent) hemolytic complement (CH50)

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent (or low) C2 levels in the presence of normal C3 and C4 values are consistent with a C2 deficiency. Low C2 levels in the presence of low C3 and C4 values are consistent with a complement-consumptive process. Low C2 and C4 values, in the presence of normal values for C3 is suggestive of C1 esterase inhibitor deficiency.

**Reference Values:**
25-47 U/mL

**Clinical References:**

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**C2 Complement, Functional, with Reflex, Serum**

**Clinical Information:** The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. This activation process results in the formation of the lytic membrane attack complex, as well as the generation of activation peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The absence of early components (C1, C2, C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to generate lytic activity or to clear immune complexes. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease, and complement deficiency may be an etiologic factor in the development of autoimmune disease. Although rare, C2 deficiency is the most common inherited complement deficiency. Homozygous C2 deficiency has an estimated prevalence ranging from 1 in 10,000 to 1 in 40,000 (the prevalence of heterozygotes is 1 in 100 to 1 in 50). Half of the homozygous patients are clinically normal. However, discoid lupus erythematosus or systemic lupus erythematosus (SLE) occurs in approximately one-third of patients with homozygous C2 deficiency. Patients with SLE and a C2 deficiency frequently have a normal anti-ds DNA titer. Clinically, many have lupus-like skin lesions and photosensitivity, but immunofluorescence studies may fail to demonstrate immunoglobulin or complement along the epidermal-dermal junction. Other diseases reported to be associated with C2 deficiency include dermatomyositis, glomerulonephritis, vasculitis, atrophoderma, cold urticaria, inflammatory bowel disease, and recurrent infections. The laboratory findings that suggest C2 deficiency include a hemolytic complement (CH50) of nearly zero, with normal values for C3 and C4.

**Useful For:** Investigation of a patient with a low (absent) hemolytic complement (CH50), with reflex testing to C3 and C4, if appropriate

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent (or low) C2 levels in the presence of normal C3 and C4 values are consistent with a C2 deficiency. Low C2 levels in the presence of low C3 and C4 values are consistent with a complement-consumptive process. Low C2 and C4 values, in the presence of normal values for C3 is suggestive of C1 esterase inhibitor deficiency.

**Reference Values:**
25-47 U/mL

**Clinical References:**
C3 Complement, Functional, Serum

**Clinical Information:** Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein [MBP]) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). The absence of early components (C1-C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to clear immune complexes or to generate lytic activity. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease and complement deficiency may be an etiologic factor in the development of autoimmune disease. C3 is at the entry point for all 3 activation pathways to activate the MAC. C3 deficiency may result in pneumococcal and neisserial infections as well as autoimmune diseases such as glomerulonephritis. Complement levels can be detected by antigen assays that quantitate the amount of the protein (C3 / Complement C3, Serum). For most of the complement proteins, a small number of cases have been described in which the protein is present but is non functional. These rare cases require a functional assay to detect the deficiency.

**Useful For:** Diagnosis of C3 deficiency Investigation of a patient with undetectable total complement (CH50) level

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C3 levels in the presence of other normal complement values are consistent with a C3 deficiency.

**Reference Values:**
21-50 U/mL


C3a Level

**Reference Values:**
0 - 780 ng/mL

C4 Acylcarnitine, Quantitative, Urine

**Clinical Information:** An isolated elevation of iso-/butyrylcarnitine (C4) in plasma or newborn screening blood spots is related to a diagnosis of either short chain acyl-CoA dehydrogenase (SCAD) deficiency or isobutyryl-CoA dehydrogenase (IBD) deficiency. Diagnostic testing, including the...
evaluation of C4 excretion in urine, is necessary to differentiate the 2 clinical entities. Patients with IBD deficiency excrete an abnormal amount of C4 acylcarnitine in urine, whereas patients with SCAD deficiency can have a normal excretion of this metabolite. The American College of Medical Genetics (ACMG) newborn screening work group published diagnostic algorithms for the follow-up of infants who had a positive newborn screening result. For more information, see http://www.acmg.net. See Newborn Screening Follow-up for Isolated C4 Acylcarnitine Elevations (also applies to any plasma C4 acylcarnitine elevation) in Special Instructions for additional information.

**Useful For:** Evaluation of patients with abnormal newborn screens showing elevations of iso-/butyrylcarnitine (C4) to aid in the differential diagnosis of short-chain acyl-CoA dehydrogenase and isobutyryl-CoA dehydrogenase deficiencies

**Interpretation:** Almost all patients with isobutyryl-CoA dehydrogenase deficiency excrete an abnormal amount of iso-/butyrylcarnitine (C4) in their urine. Some, but not all, affected individuals also excrete elevated levels of isobutyrylglycine. Conversely, patients with short-chain acyl-CoA dehydrogenase deficiency can have a normal excretion of C4. See Newborn Screening Follow-up for Isolated C4 Acylcarnitine Elevations (also applies to any plasma C4 acylcarnitine elevation) in Special Instructions for additional information.

**Reference Values:**
<3.00 millimoles/mole creatinine

**Clinical References:**

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**C4 Complement, Functional, Serum**

**Clinical Information:** Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein [MBP]) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). The absence of early components (C1-C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to generate the peptides that are necessary to clear immune complexes and to attract neutrophils or to generate to lytic activity. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease and complement deficiency may be an etiologic factor in the development of autoimmune disease. Approximately 20 cases of C4 deficiency have been reported. Most of these patients have systemic lupus erythematosus (SLE) or glomerulonephritis. Patients with C4 deficiency may also have frequent bacterial infections. Complement levels can be detected by antigen assays that quantitate the amount of the protein (C4 / Complement C4, Serum). For most of the complement proteins, a small number of cases have been described in which the protein is present but is non-functional. These rare cases require a functional assay to detect the deficiency.

**Useful For:** Diagnosis of C4 deficiency Investigation of a patient with an undetectable total complement (CH50) level

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C4 levels in the presence of normal C3 and C2 values are consistent with a C4 deficiency. Normal results indicate both normal C4 protein levels and normal functional activity. In hereditary angioedema, a disorder caused by C1 esterase inhibitor deficiency, absent or low C4 and C2 values are seen in the presence of normal C3 (due to activation and consumption of C4 and C2).
Reference Values:
22-45 U/mL


C4adep Arg Level
Reference Values:
0–2830 ng/mL

C5 Complement, Antigen, Serum
Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein, [MBP]) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). The absence of early components (C1-C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to clear immune complexes or to generate lytic activity. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease and complement deficiency may be an etiologic factor in the development of autoimmune disease. More than 30 cases of C5 deficiency have been reported. Most of these patients have neisserial infections.

Useful For: Diagnosis of C5 deficiency Investigation of a patient with an absent total complement (CH50) level

Interpretation: Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C5 levels in the presence of normal C3 and C4 values are consistent with a C5 deficiency. Absent C5 levels in the presence of low C3 and C4 values suggests complement consumption. A small number of cases have been described in which the complement protein is present but is non functional. These rare cases require a functional assay to detect the deficiency C5FX / C5 Complement, Functional, Serum.

Reference Values:
10.6-26.3 mg/dL

C5 Complement, Functional, Serum

Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein: MBP) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC and may have increased susceptibility to neisserial infections. More than 30 cases of C5 deficiency have been reported. Most of these patients have neisserial infections. Complement levels can be detected by antigen assays that quantitate the amount of the protein (C5AG / C5 Complement, Antigen, Serum). For most of the complement proteins, a small number of cases have been described in which the protein is present but is nonfunctional. These rare cases require a functional assay to detect the deficiency.

Useful For: Diagnosis of C5 deficiency Investigation of a patient with an undetectable total complement (CH50) level

Interpretation: Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C5 levels in the presence of normal C3 and C4 values are consistent with a C5 deficiency. Absent C5 levels in the presence of low C3 and C4 values suggest complement consumption. Normal results indicate both normal C5 protein levels and normal functional activity.

Reference Values: 29-53 U/mL


C5-DC Acylcarnitine, Quantitative, Urine

Clinical Information: An isolated elevation of glutarylcarnitine (C5-DC) in plasma or newborn screening blood spots is related to a diagnosis of glutaric aciduria type 1 (GA-1), also known as glutaric acidemia type 1. GA-1 is caused by a deficiency of glutaryl-CoA dehydrogenase. Urinary excretion of C5-DC is a specific biochemical marker of GA-1 that appears to be elevated even in low excretors, those patients who are affected but have normal levels of glutaric acid in urine. GA-1 is characterized by bilateral striatal brain injury leading to dystonia, often a result of acute neurologic crises triggered by illness. Many affected individuals also have macrocephaly. Dietary treatment and aggressive interventions during time of illness are recommended to try to prevent or minimize neurologic injury, which is most likely to occur in infancy and early childhood. Prevalence is approximately 1 in 100,000 individuals. The American College of Medical Genetics (ACMG) newborn screening work group published diagnostic algorithms for the follow-up of infants who had a positive newborn screening result. For more information, see http://www.acmg.net.

Useful For: Evaluation of patients with an abnormal newborn screen showing elevations of C5-DC Diagnosis of glutaric aciduria type 1 deficiency

Interpretation: Elevated excretion of C5-DC is a specific biochemical marker of glutaric aciduria type
1 that is elevated in affected patients, apparently even in low excretors or those affected individuals with normal levels of glutaric acid in urine.

**Reference Values:**

<1.54 millimoles/mole creatinine


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**C5OHU**

**C5-OH Acylcarnitine, Quantitative, Urine**

**Clinical Information:** The differential diagnosis of an isolated elevation of 3-hydroxyisovaleryl-/2-methyl-3-hydroxy acylcarnitine (C5-OH) in plasma or (newborn screening) blood spots includes the following disorders: -3-Methylcrotonyl-CoA carboxylase deficiency (common name: 3-methylcrotonylglycinuria), either infantile or maternal -3-Hydroxy 3-methylglutaryl-(HMG)-CoA lyase deficiency -Beta-ketothiolase deficiency -2-Methyl 3-hydroxybutyryl-CoA dehydrogenase deficiency -3-methylglutaconic aciduria type I -Biotinidase deficiency -Holocarboxylase deficiency Confirmatory and diagnostic testing are necessary to differentiate these clinical entities. This test can be useful in differentiating patients with 3-methylcrotonylglycinuria and with 3-methylglutaconic aciduria as they typically excrete larger amounts of C5-OH in urine compared to patients with the other diagnoses. The American College of Medical Genetics (ACMG) newborn screening work group published diagnostic algorithms for the follow-up of infants who had positive newborn screening results. For more information, see http://www.acmg.net.

**Useful For:** Evaluation of patients with an abnormal newborn screen showing elevations of 3-hydroxyisovaleryl-/2-methyl-3-hydroxybutyryl-carnitine (C5-OH)

**Interpretation:** Preliminary data showed that an elevated excretion in urine and concentration in plasma of 3-hydroxyisovaleryl-/2-methyl-3-hydroxy acylcarnitine (C5-OH) can be the only biochemical abnormalities in patients with 3-methylcrotonylglycinuria. Call 800-533-1710 for assistance in test interpretation and additional testing options.

**Reference Values:**

<2.93 millimoles/mole creatinine


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**C6FX**

**C6 Complement, Functional, Serum**

**Clinical Information:** Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein [MBP]) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC, and may have increased susceptibility to neisserial infections. A number of patients with C6 deficiency have been reported, and the majority of these patients are South African. Most of these patients have systemic meningococcal infection and some have had invasive gonococcal infections. Normal levels of C6 antigen have been reported in patients with dysfunctional C6 lytic activity.

**Useful For:** Diagnosis of C6 deficiency Investigation of a patient with an undetectable total
Complement (CH50) level

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (e.g., as a consequence of infectious or autoimmune processes). Absent C6 levels in the presence of normal C3 and C4 values are consistent with a C6 deficiency. Absent C6 levels in the presence of low C3 and C4 values suggest complement consumption. Normal results indicate both normal C6 protein levels and normal functional activity.

**Reference Values:**
32-57 U/mL

**Clinical References:**

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**Complement, Functional, Serum**

**Clinical Information:** Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein; MBP) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC, and may have increased susceptibility to neisserial infections. The majority of cases of C7 deficiency have neisserial infections, but cases of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), scleroderma, and pyoderma gangrenosum have been reported. The pathogenesis of the rheumatic disease is not clear. Complement levels can be detected by antigen assays that quantitate the amount of the protein. For most of the complement proteins, a small number of cases have been described in which the protein is present but is non-functional. These rare cases require a functional assay to detect the deficiency.

**Useful For:** Diagnosis of C7 deficiency Investigation of a patient with an undetectable total complement (CH50) level

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (e.g., as a consequence of infectious or autoimmune processes). Absent C7 levels in the presence of normal C3 and C4 values are consistent with a C7 deficiency. Absent C7 levels in the presence of low C3 and C4 values suggest complement consumption.

**Reference Values:**
36-60 U/mL

**Clinical References:**
C8 Complement, Functional, Serum

Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein [MBP]) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC, and may have increased susceptibility to neisserial infections. Most patients with C8 deficiency have invasive neisserial infections. For most of the complement proteins, a small number of cases have been described in which the protein is present but is non-functional. These rare cases require a functional assay to detect the deficiency.

Useful For: Diagnosis of C8 deficiency Investigation of a patient with an undetectable total hemolytic complement (CH50) level

Interpretation: Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C8 levels in the presence of normal C3 and C4 values are consistent with a C8 deficiency. Absent C8 levels in the presence of low C3 and C4 values suggests complement consumption. Normal results indicate both normal C8 protein levels and normal functional activity.

Reference Values: 33-58 U/mL


C9 Complement, Functional, Serum

Clinical Information: Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: 1) the classic pathway, 2) the alternative (or properdin) pathway, and 3) the lectin activation (mannan-binding protein [MBP]) pathway. The classic pathway of the complement system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC, and may have increased susceptibility to neisserial infections. C9 deficiency is common in the Japanese population and has been reported to occur in almost 1% of the population. The lytic activity of C9-deficient serum is decreased. However, the assembly of C5b-C8 complexes will result in a transmembrane channel with lytic activity, although the lytic activity is reduced. Many C9-deficient patients are therefore asymptomatic. C9-deficient patients may, however, present with invasive neisserial infections. Complement levels can be detected by antigen assays that quantitate the amount of
the protein. For most of the complement proteins, a small number of cases have been described in which the protein is present but is non functional. These rare cases require a functional assay to detect the deficiency.

**Useful For:** Diagnosis of C9 deficiency Investigation of a patient with a low total (hemolytic) complement (CH50) level

**Interpretation:** Low levels of complement may be due to inherited deficiencies, acquired deficiencies, or due to complement consumption (eg, as a consequence of infectious or autoimmune processes). Absent C9 levels in the presence of normal C3 and C4 values are consistent with a C9 deficiency. Absent C9 levels in the presence of low C3 and C4 values suggests complement consumption. Normal results indicate both normal C9 protein levels and normal functional activity.

**Reference Values:**
37-61 U/mL

**Clinical References:**

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**C9orf72 Hexanucleotide Repeat, Molecular Analysis**

**Clinical Information:** Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease affecting the upper and lower motor neurons. The disease is characterized by progressive spasticity, muscle wasting and paralysis, typically leading to death from respiratory failure. Frontotemporal dementia (FTD) is a dementia syndrome that predominantly involves the frontal and temporal lobes of the brain. Clinical presentation is variable and includes progressive changes in behavior and personality and language disturbances. Affected individuals may also exhibit extrapyramidal signs. ALS and FTD are now thought to represent an overlapping spectrum of disease. Recent literature has found that approximately 40% of familial ALS, 25% of familial FTD, and 90% of familial ALS/FTD cases have a large hexanucleotide repeat (GGGGCC) expansion in a noncoding region of C9orf72. At lower frequency, C9orf72 hexanucleotide repeat expansions have also been observed in individuals with sporadic ALS, FTD, and ALS/FTD. The vast majority of individuals affected with a C9orf72-related disorder (c9ALS, c9FTD, or c9ALS/FTD) have hexanucleotide repeat expansions in the hundreds to thousands, while unaffected individuals have repeat sizes less than 20. The significance of repeat sizes between 20 and 100 repeats is currently unclear as both healthy controls and individuals with ALS and/or FTD phenotypes have been reported with repeat sizes in this range.

**Useful For:** Molecular confirmation of clinically suspected cases of c9FTD/ALS, frontotemporal dementia (FTD), or amyotrophic lateral sclerosis (ALS) Presymptomatic testing for individuals with a family history of c9FTD/ALS and a documented expansion in the C9orf72 gene

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Normal alleles (reference):<20 GGGGCC repeats
Indeterminate alleles: 20-100 GGGGCC repeats
Pathogenic alleles: >100* GGGGCC repeats

*The exact cutoff for pathogenicity is currently undefined. Although additional studies are needed to confirm if 100 repeats is the cutoff for pathogenicity, most individuals affected with a C9orf72-related disorder have C9orf72 hexanucleotide repeat expansions with hundreds to thousands of repeats.
An interpretive report will be provided.

**Clinical References:**

**Cabbage IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Cabbage, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and...
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
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<td>4</td>
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<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>
| 6     | > or =100 | Strongly positive | Reference values apply to all ages.


**Cocoa/Cocoa, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens responsible for anaphylaxis, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
### Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>Interpretation</th>
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<tbody>
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<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69 Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49 Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4 Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9 Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9 Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

### Clinical References:


### Cadmium for Occupational Monitoring, Blood

**Clinical Information:** The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of chronic exposure comes from spray painting of organic-based paints without use of a protective breathing apparatus; auto repair mechanics represent a susceptible group for cadmium toxicity. Tobacco smoke is another common source of cadmium exposure.

**Useful For:** Detecting exposure to cadmium, a toxic heavy metal

**Interpretation:** Normal blood cadmium is <5.0 mcg/L, with most results in the range of 0.5 to 2.0 mcg/L. Acute toxicity will be observed when the blood level exceeds 50 mcg/L.

**Reference Values:**

0.0-4.9 mcg/L

Reference values apply to all ages.

**Clinical References:**


### Cadmium Occupational Exposure, Random, Urine

**Clinical Information:** The toxicity of cadmium resembles the other heavy metals (arsenic, mercury and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric acid also occur over a period of years, and precede overt renal failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of cadmium exposure is tobacco smoke, which has been implicated as the primary sources of the metal leading to reproductive toxicity in both males and females. Chronic exposure to cadmium causes accumulated renal damage. The excretion of cadmium is proportional to creatinine except when renal damage has occurred. Renal damage due to cadmium exposure can be detected by increased cadmium excretion relative to
creatinine. The Occupational Safety and Health Administration (OSHA) mandated (Fed Reg 57:42,102-142,463, September 1992) that all monitoring of employees exposed to cadmium in the workplace should be done using the measurement of urine cadmium and creatinine, expressing the results of mcg of cadmium per gram of creatinine.

**Useful For:** Detecting occupational exposure to cadmium in random urine specimens

**Interpretation:** Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. Results above 15 mcg/g creatinine are considered indicative of severe exposure

**Reference Values:**
Only orderable as part of profile. See CDUO / Cadmium Occupational Exposure, Random, Urine or HMSOR / Heavy Metals Occupational Exposure with Reflex, Urine.

**Clinical References:**

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**CDUO 48553**

**Cadmium Occupational Exposure, Random, Urine**

**Clinical Information:** The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric acid also occur over a period of years, and precede overt renal failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of cadmium exposure is tobacco smoke, which has been implicated as the primary sources of the metal leading to reproductive toxicity in both males and females. Chronic exposure to cadmium causes accumulated renal damage. The excretion of cadmium is proportional to creatinine except when renal damage has occurred. Renal damage due to cadmium exposure can be detected by increased cadmium excretion relative to creatinine. The Occupational Safety and Health Administration (OSHA) mandated (Fed Reg 57:42,102-142,463, September 1992) that all monitoring of employees exposed to cadmium in the workplace should be done using the measurement of urine cadmium and creatinine, expressing the results of mcg of cadmium per gram of creatinine.

**Useful For:** Detecting occupational exposure to cadmium, a toxic heavy metal in random urine specimens

**Interpretation:** Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. Results above >15 mcg/g creatinine are considered indicative of severe exposure.

**Reference Values:**
Biological Exposure Indices (BEI)

<5.0 mcg/g creatinine

**Clinical References:**

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**CDU 8678**

**Cadmium, 24 Hour, Urine**

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Clinical Information: The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric acid also occur over a period of years, and precede overt renal failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of chronic exposure comes from spray painting of organic-based paints without use of a protective breathing apparatus; auto repair mechanics represent a susceptible group for cadmium toxicity. Another common source of cadmium exposure is tobacco smoke, which has been implicated as the primary source of the metal leading to reproductive toxicity in both males and females. The concentration of cadmium in the kidneys and in the urine is elevated in some patients exposed to cadmium. See also CDOM / Cadmium for Occupational Monitoring, Urine. If employees are being monitored in the workplace, the Occupational Safety and Health Administration requires that laboratory reports express the cadmium excretion rate per gram of creatinine rather than per 24 hours. This alternative test is available to accommodate that requirement. Mayo Medical Laboratories is certified to provide this test.

Useful For: Detecting exposure to cadmium, a toxic heavy metal in 24-hour urine specimens

Interpretation: Normally, the excretion of cadmium is proportional to creatinine. When renal damage has occurred, cadmium excretion increases relative to creatinine.

Reference Values:
0-17 years: not established
> or =18 years: <0.6 mcg/24 hour


Cadmium, Blood

Clinical Information: The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of chronic exposure comes from spray painting of organic-based paints without use of a protective breathing apparatus; auto repair mechanics represent a susceptible group for cadmium toxicity. In addition, another common source of cadmium exposure is tobacco smoke.

Useful For: Detecting exposure to cadmium, a toxic heavy metal

Interpretation: Normal blood cadmium is <5.0 ng/mL, with most results in the range of 0.5 to 2.0 ng/mL. Acute toxicity will be observed when the blood level exceeds 50 ng/mL.

Reference Values:
0.0-4.9 ng/mL
Reference values apply to all ages.

**Clinical Information:** The toxicity of cadmium resembles the other heavy metals (arsenic, mercury and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric acid also occur over a period of years, and precede overt renal failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of cadmium exposure is tobacco smoke, which has been implicated as the primary sources of the metal leading to reproductive toxicity in both males and females. Chronic exposure to cadmium causes accumulated renal damage. The excretion of cadmium is proportional to creatinine except when renal damage has occurred. Renal damage due to cadmium exposure can be detected by increased cadmium excretion relative to creatinine. The Occupational Safety and Health Administration (OSHA) mandated (Fed Reg 57:42,102-142,463, September 1992) that all monitoring of employees exposed to cadmium in the workplace should be done using the measurement of urine cadmium and creatinine, expressing the results of mcg of cadmium per gram of creatinine.

**Useful For:** Detecting exposure to cadmium, a toxic heavy metal in random urine specimens

**Interpretation:** Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. Results above 15 mcg/g creatinine are considered indicative of severe exposure.

**Reference Values:**

0-17 years: not established

> or =18 years: <0.6 mcg/g creatinine

**Clinical References:**

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**Cadmium/Creatinine Ratio, Urine**

**Clinical Information:** The toxicity of cadmium resembles the other heavy metals (arsenic, mercury and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric acid also occur over a period of years, and precede overt renal failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of cadmium exposure is tobacco smoke, which has been implicated as the primary sources of the metal leading to reproductive toxicity in both males and females. Chronic exposure to cadmium causes accumulated renal damage. The excretion of cadmium is proportional to creatinine except when renal damage has occurred. Renal damage due to cadmium exposure can be detected by increased cadmium excretion relative to creatinine. The Occupational Safety and Health Administration (OSHA) mandated (Fed Reg 57:42,102-142,463, September 1992) that all monitoring of employees exposed to cadmium in the workplace should be done using the measurement of urine cadmium and creatinine, expressing the results of mcg of cadmium per gram of creatinine.

**Useful For:** Detecting exposure to cadmium, in random urine specimens

**Interpretation:** Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. Results above 15 mcg/g creatinine are considered indicative of severe exposure.

**Reference Values:**

Only orderable as part of profile. See CDRCR / Cadmium/Creatinine Ratio, Random, Urine or HMCRU / Heavy Metal/Creatinine Ratio, with Reflex, Urine.

**Clinical References:**
CAFN 37034  
**Caffeine, Serum**

**Clinical Information:** Caffeine is used to treat apnea that occurs in newborn infants, the most frequent complication seen in the neonatal nursery. Caffeine is administered orally (nasogastric tube) as a loading dose of 3 mg/kg followed by a maintenance dose of 1 mg/kg administered once every 24 to 48 hours, depending on the patient's response and the serum level. In neonates, caffeine has a half-life that ranges from 20 to 100 hours, which is much longer than in adults (typically 4-6 hours) due to the immaturity of the neonatal liver. This requires that small doses be administered at much longer intervals than would be predicted based on adult pharmacokinetics. The volume of distribution of caffeine is 0.6 L/kg and the drug is approximately 35% protein bound. Toxicity observed in neonates is characterized by central nervous system and skeletal muscle stimulation and bradycardia. These symptoms are seen in adults at lower levels than in neonates, suggesting that neonates have much greater tolerance to the drug.

**Useful For:** Monitoring therapy in neonates Assessing toxicity in neonates

**Interpretation:** Optimal pharmacologic response occurs when the serum level is in the range of 8.0 to 20.0 mcg/mL. Toxicity in neonates and adults may be seen when the serum level is >20.0 mcg/mL.

**Reference Values:**
- Therapeutic: 8.0-20.0 mcg/mL
- Critical value: > or ≥30.0 mcg/mL

**Clinical References:** Ou CN, Frawley VL: Concurrent measurement of theophylline and caffeine in neonates by an interference-free liquid-chromatographic method. Clin Chem 1983;29:1934-1936

CALCI 70368  
**Calcitonin (CALCI) Immunostain, Technical Component Only**

**Clinical Information:** Calcitonin is a hormone involved in calcium metabolism. Staining for calcitonin produces fine granular, cytoplasmic staining of C cells of thyroid, medullary thyroid carcinomas, many atypical laryngeal carcinoids, and other neuroendocrine tumors. Amyloid deposits within medullary thyroid carcinoma may also exhibit varying degrees of calcitonin immunoreactivity.

**Useful For:** Aids in the identification of C cells of thyroid, medullary thyroid carcinomas, many atypical laryngeal carcinoids, and other neuroendocrine tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Calcitonin, Fine-Needle Aspiration Biopsy (FNAB)-Needle Wash, Lymph Node

Clinical Information: Calcitonin is a polypeptide hormone secreted by the parafollicular cells (also referred to as calcitonin cells or C-cells) of the thyroid gland. Malignant tumors arising from thyroid C-cells (medullary thyroid carcinoma: MTC) usually produce elevated levels of calcitonin. MTC is an uncommon malignant thyroid tumor, comprising less than 5% of all thyroid malignancies. Measurement of serum calcitonin is used in the follow-up of patients who underwent surgical removal of the thyroid gland. Studies have reported that the measurement of calcitonin in fine-needle aspiration biopsy (FNAB)-needle washes improves the evaluation of suspicious lymph nodes in patients with a history of MTC when used in combination with cytology. Comparing the results of calcitonin in the needle rinse with serum calcitonin is highly recommended. An elevated calcitonin in the serum could falsely elevate calcitonin in the washings, if the rinse is contaminated with blood. In these cases only calcitonin values significantly higher than the serum should be considered as true-positives. Cytologic examination and measurement of calcitonin can be performed on the same specimen. To measure calcitonin, the FNA needle is rinsed with a small volume of normal saline solution immediately after a specimen for cytological examination (for a smear or CytoTrap preparation) has been expelled from the needle. Calcitonin levels are measured in the needle wash.

Useful For: As an adjunct to cytologic examination of fine-needle aspiration specimens in athyrotic individuals treated for medullary thyroid carcinoma to confirm or exclude metastases in enlarged or ultrasonographically suspicious lymph nodes

Interpretation: In athyrotic patients with a history of medullary thyroid carcinoma (MTC), a fine-needle aspiration calcitonin value of 5.0 pg/mL and greater is suggestive of the presence of metastatic MTC in the biopsied lymph node. Calcitonin values less than 5.0 pg/mL suggest the lymph node does not contain medullary thyroid carcinoma. This result is dependent on accurate sampling and a total needle wash volume of less than or equal to 1.5 mL. This test should be interpreted in the context of the clinical presentation, imaging and cytology findings. If the results are discordant with the clinical presentation, a sampling error at the time of biopsy should be considered.

Reference Values:
An interpretive report will be provided.


Calcitonin, Serum

Clinical Information: Calcitonin is a polypeptide hormone secreted by the parafollicular cells (also referred to as calcitonin cells or C cells) of the thyroid gland. The main action of calcitonin is the inhibition of bone resorption by regulating the number and activity of osteoclasts. Calcitonin is secreted in direct response to serum hypercalcemia and may prevent large oscillations in serum calcium levels and excessive loss of body calcium. However, in comparison to parathyroid hormone and 1,25-dihydroxyvitamin D, the role of calcitonin in the regulation of serum calcium in humans is minor. Measurements of serum calcitonin levels are, therefore, not useful in the diagnosis of disorders of calcium homeostasis. Malignant tumors arising from thyroid C cells (medullary thyroid carcinoma: MTC) usually produce elevated levels of calcitonin. MTC is an uncommon malignant thyroid tumor, comprising less than 5% of all thyroid malignancies. Approximately 25% of these cases are familial, usually appearing as a component of multiple endocrine neoplasia type II (MENII, Sipple syndrome). MTC may also occur in families without other associated endocrine dysfunction, with similar autosomal dominant transmission as
MENII, which is then called familial medullary thyroid carcinoma (FMTC). Mutations in the RET proto-oncogene are associated with MENII and FMTC. Serum calcitonin concentrations are high in infants, decline rapidly, and are relatively stable from childhood through adult life. In general, calcitonin serum concentrations are higher in men than in women due to the larger C-cell mass in men. Serum calcitonin concentrations may be increased in patients with chronic renal failure, and other conditions such as hyperparathyroidism, leukemic and myeloproliferative disorders, Zollinger-Ellison syndrome, autoimmune thyroiditis, small cell and large cell lung cancers, breast and prostate cancer, mastocytosis, and various neuroendocrine tumors, in particular, islet cell tumors.

**Useful For:** Aids in the diagnosis and follow-up of medullary thyroid carcinoma Aids in the evaluation of multiple endocrine neoplasia type II and familial medullary thyroid carcinoma

**Interpretation:** Although most patients with sporadic medullary thyroid carcinoma (MTC) have high basal serum calcitonin concentrations, 30% of those with familial MTC or multiple endocrine neoplasia type II (MENII) have normal basal levels. In completely cured cases following surgical therapy for MTC, serum calcitonin levels fall into the undetectable range over a variable period of several weeks. Persistently elevated postoperative serum calcitonin levels usually indicate incomplete cure. The reasons for this can be locoregional lymph node spread or distant metastases. In most of these cases, imaging procedures are required for further workup. Those individuals who are then found to suffer only locoregional spread may benefit from additional surgical procedures. However, the survival benefits derived from such approaches are still debated. A rise in previously undetectable or very low postoperative serum calcitonin levels is highly suggestive of disease recurrence or spread, and should trigger further diagnostic evaluations.

**Reference Values:**

**Pediatric**
- 1 month: < or = 34 pg/mL
- 2 months: < or = 31 pg/mL
- 3 months: < or = 28 pg/mL
- 4 months: < or = 26 pg/mL
- 5 months: < or = 24 pg/mL
- 6 months: < or = 22 pg/mL
- 7 months: < or = 20 pg/mL
- 8 months: < or = 19.0 pg/mL
- 9 months: < or = 17.0 pg/mL
- 10 months: < or = 16.0 pg/mL
- 11 months: < or = 15.0 pg/mL
- 12-14 months: < or = 14.0 pg/mL
- 15-17 months: < or = 12.0 pg/mL
- 18-20 months: < or = 10.0 pg/mL
- 21-23 months: < or = 9.0 pg/mL
- 2 years: < or = 8.0 pg/mL
- 3-9 years: < or = 7.0 pg/mL
- 10-15 years: < or = 6.0 pg/mL
- 16 years: < or = 5.0 pg/mL

**Adults**
- 17 years and older:
  - Males: < or = 14.3 pg/mL
  - Females: < or = 7.6 pg/mL

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.

**Calcium, 24 Hour, Urine**

**Clinical Information:** Calcium is the fifth most common element in the body. It is a fundamental element necessary to form electrical gradients across membranes, an essential cofactor for many enzymes, and the main constituent in bone. Under normal physiologic conditions, the concentration of calcium in serum and in cells is tightly controlled. Calcium is excreted in both urine and feces. Ordinarily about 20% to 25% of dietary calcium is absorbed and 98% of filtered calcium is reabsorbed in the kidney. Traffic of calcium between the gastrointestinal tract, bone, and kidney is tightly controlled by a complex regulatory system that includes vitamin D and parathyroid hormone. Sufficient bioavailable calcium is essential for bone health. Excessive excretion of calcium in the urine is a common contributor to kidney stone risk.

**Useful For:** Evaluation of calcium oxalate and calcium phosphate kidney stone risk, and calculation of urinary supersaturations. Evaluation of bone diseases, including osteoporosis and osteomalacia.

**Interpretation:** Increased urinary calcium excretion (hypercalciuria) is a known contributor to kidney stone disease and osteoporosis. Many cases are genetic (often termed "idiopathic"). Previously such patients were often divided into fasting versus absorptive hypercalciuria depending on the level of urine calcium in a fasting versus fed state, but the clinical utility of this approach is now in question. Overall, the risk of stone disease appears increased when 24-hour urine calcium is >250 mg in men and >200 mg in women. Thiazide diuretics are often used to reduce urinary calcium excretion, and repeat urine collections can be performed to monitor the effectiveness of therapy. Known secondary causes of hypercalciuria include hyperparathyroidism, Paget disease, prolonged immobilization, vitamin D intoxication, and diseases that destroy bone (such as metastatic cancer or multiple myeloma). Urine calcium excretion can be used to gauge the adequacy of calcium and vitamin D supplementation, for example in states of gastrointestinal fat malabsorption that are associated with decreased bone mineralization (osteomalacia).

**Reference Values:**
- Males: <250 mg/24 hours
- Females: <200 mg/24 hours

- Reference values have not been established for patients <18 years and >83 years of age.
- Reference values apply to 24-hour collection.

**Clinical References:**

**Calcium, Ionized, Serum**

**Clinical Information:** Ionized calcium, which accounts for 50% to 55% of total calcium, is the physiologically active form of calcium. Low ionized calcium values are often seen in renal disease, critically ill patients, or patients receiving rapid transfusion of citrated whole blood or blood products. Increased serum ionized calcium concentrations may be seen with primary hyperparathyroidism, ectopic parathyroid hormone-producing tumors, excess intake of vitamin D, or various malignancies. Nomograms have been used to calculate ionized calcium from total calcium, albumin, and pH values. However, calculated ionized calcium results have proven to be unsatisfactory. A Mayo study of 114 patients found significant differences between ionized and total calcium in 26% of patients.

**Useful For:** Assessing calcium states during liver transplantation surgery, cardiopulmonary bypass, or any procedure requiring rapid transfusion of whole blood in neonates and critically ill patients. Second-order test in the evaluation of patients with abnormal calcium values.
Interpretation: Serum ionized calcium concentrations 50% below normal will result in severely reduced cardiac stroke work. With moderate to severe hypocalcemia, left ventricular function may be profoundly depressed. Ionized calcium values are higher in children and young adults. Ionized calcium result has been adjusted to pH 7.40 to account for changes in specimen pH that may occur during transport. Ionized calcium concentration increases approximately 0.2 mg/dL per 0.1 pH unit decrease.

Reference Values:
IONIZED CALCIUM
< or =13 days old: not established
14 days-<1 year: 5.21-5.99 mg/dL
1-<2 years: 5.04-5.84 mg/dL
2-<3 years: 4.87-5.67 mg/dL
3-<24 years: 4.83-5.52 mg/dL
24-< or =97 years: 4.57-5.43 mg/dL
> or =98 years: not established

pH
< or =13 days old: not established
14 days-97 years old: 7.35-7.48
> or =98 years old: not established

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.


CACR1 63450
Calcium, Random, Urine

Clinical Information: Calcium is the fifth most common element in the body. It is a fundamental element necessary to form electrical gradients across membranes, an essential cofactor for many enzymes, and the main constituent in bone. Under normal physiologic conditions, the concentration of calcium in serum and in cells is tightly controlled. Calcium is excreted in both urine and feces. Ordinarily about 20% to 25% of dietary calcium is absorbed and 98% of filtered calcium is reabsorbed in the kidney. Traffic of calcium between the gastrointestinal tract, bone, and kidney is tightly controlled by a complex regulatory system that includes vitamin D and parathyroid hormone. Sufficient bioavailable calcium is essential for bone health. Excessive excretion of calcium in the urine is a common contributor to kidney stone risk.

Useful For: Evaluation of calcium oxalate and calcium phosphate kidney stone risk, and calculation of urinary supersaturations Evaluation of bone diseases, including osteoporosis and osteomalacia

Interpretation: Increased urinary calcium excretion (hypercalciuria) is a known contributor to kidney stone disease and osteoporosis. Many cases are genetic (often termed "idiopathic"). Previously such patients were often divided into fasting versus absorptive hypercalciuria depending on the level of urine calcium in a fasting versus fed state, but the clinical utility of this approach is now in question. Overall, the risk of stone disease appears increased when 24-hour urine calcium is >250 mg in men and >200 mg in women. Thiazide diuretics are often used to reduce urinary calcium excretion, and repeat urine collections can be performed to monitor the effectiveness of therapy. Known secondary causes of hypercalciuria include hyperparathyroidism, Paget disease, prolonged immobilization, vitamin D intoxication, and diseases that destroy bone (such as metastatic cancer or multiple myeloma). Urine calcium excretion can be used to gauge the adequacy of calcium and vitamin D supplementation, for example in states of gastrointestinal fat malabsorption that are associated with decreased bone mineralization (osteomalacia).

Reference Values:
Random Calcium/Creatinine Ratio: <0.20 mg/mg
Reference values have not been established for patients <18 years and >83 years of age.


**CACR2 Calcium, Random, Urine**

**Reference Values:**
Only orderable as part of a profile. For more information see SSATR Supersaturation Profile, Pediatric, Random, Urine.

**CA Calcium, Total, Serum**

**Clinical Information:** The calcium content of an adult is somewhat over 1 kg (about 2% of the body weight). Of this, 99% is present as calcium hydroxyapatite in bones and less than 1% is present in the extra-osseous intracellular space or extracellular space (ECS). The calcium level in the ECS is in dynamic equilibrium with the rapidly exchangeable fraction of bone calcium. In serum, calcium is bound to a considerable extent to proteins (approximately 40%), 10% is in the form of inorganic complexes, and 50% is present as free or ionized calcium. Calcium ions affect the contractility of the heart and the skeletal musculature, and are essential for the function of the nervous system. In addition, calcium ions play an important role in blood clotting and bone mineralization. Hypocalcemia is due to the absence or impaired function of the parathyroid glands or impaired vitamin-D synthesis. Chronic renal failure is also frequently associated with hypocalcemia due to decreased vitamin-D synthesis as well as hyperphosphatemia and skeletal resistance to the action of parathyroid hormone (PTH). Characteristic symptoms of hypocalcemia are latent or manifest tetany and osteomalacia. Hypercalcemia is brought about by increased mobilization of calcium from the skeletal system or increased intestinal absorption. The majority of cases are due to primary hyperparathyroidism (pHPT) or bone metastasis of carcinoma of the breast, prostate, thyroid gland, or lung. Patients who have pHPT and bone disease, renal stones or nephrocalcinosis, or other signs or symptoms are candidates for surgical removal of the parathyroid glands. Severe hypercalcemia may result in cardiac arrhythmia. Calcium levels may also reflect abnormal vitamin D or protein levels

**Useful For:** Diagnosis and monitoring of a wide range of disorders including diseases of bone, kidney, parathyroid gland, or gastrointestinal tract

**Interpretation:** Hypocalcemia: Long-term therapy must be tailored to the specific disease causing the hypocalcemia. The therapeutic endpoint is to achieve a serum calcium level of 8.0 to 8.5 mg/dL to prevent tetany. For symptomatic hypocalcemia, calcium may be administered intravenously. Hypercalcemia: The level at which hypercalcemic symptoms occur varies from patient to patient. Symptoms are common when serum calcium levels are above 11.5 mg/dL, although patients may be asymptomatic at this level. Levels above 12.0 mg/dL are considered a critical value in the Mayo Health System. Severe hypercalcemia (>15.0 mg/dL) is a medical emergency.

**Reference Values:**
<1 year: 8.7-11.0 mg/dL
1-17 years: 9.3-10.6 mg/dL
18-59 years: 8.6-10.0 mg/dL
60-90 years: 8.8-10.2 mg/dL
>90 years: 8.2-9.6 mg/dL


Caldesmon Immunostain, Technical Component Only

**Clinical Information:** Caldesmon is a smooth muscle specific protein that regulates smooth muscle contraction. This clone recognizes the high-molecular-weight variant (h-caldesmon) and does not react with the nonmuscle variant. Neither variant of caldesmon is present in skeletal muscle. Anti-h-caldesmon seems to be a reliable marker of smooth muscle differentiation, and may assist in the diagnosis of smooth muscle tumors.

**Useful For:** A marker of smooth muscle differentiation

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


California Virus (La Crosse) Encephalitis Antibody Panel, IgG and IgM, Spinal Fluid

**Clinical Information:** California (La Crosse) virus is a member of the Bunyaviridae family and it is one of the arthropod-borne encephalitides. It is transmitted by various Aedes and Culex mosquitoes and is found in such intermediate hosts as the rabbit, squirrel, chipmunk, and field mouse. California meningoencephalitis is usually mild and occurs in late summer. Ninety percent of infections are seen in children under 15 years of age, usually from rural areas. The incubation period is estimated to be 7 days and acute illness lasts 10 days or less in most instances. Typically, the first symptoms are nonspecific, lasting 1 to 3 days, and are followed by the appearance of central nervous system signs and symptoms such as stiff neck, lethargy, and seizures, which usually abate within 1 week. Symptomatic infection is almost never recognized in those over 18 years old. The most important sequelae of California virus encephalitis is epilepsy, which occurs in about 10% of children; almost always in patients who have had seizures during the acute illness. A few patients (estimated 2%) have persistent paresis. Learning disabilities or other objective cognitive deficits have been reported in a small proportion (<2%) of patients. Learning performance and behavior of most recovered patients are not distinguishable from comparison groups in these same areas. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age, sex, and occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age. Serious California (La Crosse) virus infections primarily involve children, especially boys. Adult males exposed to California viruses...
have high prevalence rates of antibody but usually show no serious illness. Infection among males is primarily due to working conditions and sports activities taking place where the vector is present.

**Useful For:** Aiding the diagnosis of California (La Crosse) encephalitis

**Interpretation:** A positive result indicates intrathecal synthesis of antibody and is indicative of neurological infection.

**Reference Values:**
- IgG: <1:10
- IgM: <1:10

Reference values apply to all ages.

**Clinical References:**

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**CAVP 83153**

**California Virus (La Crosse) IgG and IgM, Serum**

**Clinical Information:** California virus (La Crosse) is a member of the Bunyaviridae family and is one of the arthropod-borne encephalitides. It is transmitted by various Aedes and Culex mosquitoes and is found in such intermediate hosts as the rabbit, chipmunk, and field mouse. California meningoencephalitis is usually mild and occurs in late summer. Ninety percent of infections are seen in children under 15 years of age, usually from rural areas. The incubation period is estimated to be 7 days and acute illness lasts 10 days or less in most instances. Typically, the first symptoms are nonspecific, lasting 1 to 3 days, and are followed by the appearance of central nervous system signs and symptoms such as stiff neck, lethargy, and seizures, which usually abate within 1 week. Symptomatic infection is almost never recognized in those over 18 years old. The most important sequelae of California virus encephalitis is epilepsy, which occurs in about 10% of children; almost always in patients who have had seizures during the acute illness. A few patients (estimated 2%) have persistent paresis. Learning disabilities or other objective cognitive deficits have been reported in a small proportion (no more than 2%) of patients. Learning performance and behavior of most recovered patients are not distinguishable from comparison groups in these same areas. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age, sex, and occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age. Serious California (La Crosse) virus infections primarily involve children, especially boys. Adult males exposed to California viruses have high prevalence rates of antibody but usually show no serious illness. Infection among males is primarily due to working conditions and sports activities taking place where the vector is present.

**Useful For:** Aiding the diagnosis of California virus (La Crosse)

**Interpretation:** In patients infected with these or related viruses, IgG antibody is generally detectable within 1 to 3 weeks of onset, peaking within 1 to 2 months and declining slowly thereafter. IgM class antibody is also reliably detected within 1 to 3 weeks of onset, peaking and rapidly declining within 3 months. Single serum specimen IgG of 1:10 or greater indicates exposure to the virus. Results from a single serum specimen can differentiate early (acute) infection from past infection with immunity if IgM is positive (suggests acute infection). A 4-fold or greater rise in IgG antibody titer in acute and convalescent sera indicates recent infection.

**Reference Values:**
- IgG: <1:10
- IgM: <1:10

Reference values apply to all ages.

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**CALPN 70370**

**Calponin Immunostain, Technical Component Only**

**Clinical Information:** Calponin is a cytoskeleton-associated protein that can bind to actin, tropomyosin, troponin C, and calmodulin, and is involved in modulation of smooth muscle contraction. Calponin is expressed in smooth muscle cells and myoepithelial cells.

**Useful For:** Marker of myoepithelium

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**CALPR 63016**

**Calprotectin, Feces**

**Clinical Information:** Calprotectin, formed as a heterodimer of S100A8 and S100A9, is a member of the S100 calcium-binding protein family. It is expressed primarily by granulocytes and, to a lesser degree, by monocytes/macrophages and epithelial cells. In neutrophils, calprotectin comprises almost 60% of the total cytoplasmic protein content. Activation of the intestinal immune system leads to recruitment of cells from the innate immune system, including neutrophils. The neutrophils are then activated, which leads to release of cellular proteins, including calprotectin. Calprotectin eventually translocates across the epithelial barrier and enters the lumen of the gut. As the inflammatory process progresses, the released calprotectin is absorbed by the fecal material before it is excreted from the body. The amount of calprotectin present in the feces is proportional to the number of neutrophils within the gastrointestinal mucosa and can be used as an indirect marker of intestinal inflammation. Calprotectin is most frequently used as part of the diagnostic evaluation of patients with suspected inflammatory bowel disease (IBD). Patients with IBD may be diagnosed with Crohn disease or ulcerative colitis. Although distinct in their pathology and clinical manifestations, both are associated with significant intestinal inflammation. Elevated concentrations of fecal calprotectin may be useful in distinguishing IBD from functional gastrointestinal disorders, such as irritable bowel syndrome (IBS). When used for this differential diagnosis, fecal calprotectin has sensitivity and specificity both of approximately 85%. However, it must be remembered that increases in fecal calprotectin are not diagnostic for IBD, as other disorders such as celiac disease, colorectal cancer, and gastrointestinal

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infections, may also be associated with neutrophilic inflammation.

**Useful For:** Evaluation of patients suspected of having a gastrointestinal inflammatory process. Distinguishing inflammatory bowel disease (IBD) from irritable bowel syndrome (IBS), when used in conjunction with other diagnostic modalities, including endoscopy, histology, and imaging.

**Interpretation:** Calprotectin concentrations of 50.0 mcg/g and lower are not suggestive of an active inflammatory process within the gastrointestinal system. For patients experiencing gastrointestinal symptoms, consider further evaluation for functional gastrointestinal disorders. Calprotectin concentrations between 50.1 and 120.0 mcg/g are borderline and may represent a mild inflammatory process, such as in treated inflammatory bowel disease (IBD) or associated with NSAID or aspirin usage. For patients with clinical symptoms suggestive of IBD, retesting in 4 to 6 weeks may be indicated. Calprotectin concentrations of 120.1 mcg/g and higher are suggestive of an active inflammatory process within the gastrointestinal system. Further diagnostic testing to determine the etiology of the inflammation is suggested.

**Reference Values:**
- < 50.0 mcg/g (Normal)
- 50.1-120.0 mcg/g (Borderline)
- > 120.1 mcg/g (Abnormal)

Reference values apply to all ages.

**Clinical References:**

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**CALR Mutation Analysis, Myeloproliferative Neoplasm (MPN)**

**Clinical Information:** The most frequent genetic mutation in BCR-ABL1-negative myeloproliferative neoplasm (MPN), essential thrombocythemia (ET), and primary myelofibrosis (PMF) is the JAK2V617F mutation, which is present in approximately 50% to 60% of patients. It serves as a confirmatory molecular marker of these diseases. Mutations in the MPL gene are found in an additional 5% to 10% of ET and PMF cases. It was recently discovered that somatic mutation (insertions and deletions) in exon 9 of the CALR gene is the second most frequent somatic mutation after JAK2 in ET and PMF patients, and it is mutually exclusive of JAK2 and MPL mutations. It has a frequency of approximately 49% to 88% in JAK2 and MPL-wild type (WT) ET and PMF, and is not found in polycythemia vera (PV) patients. Therefore, CALR mutation serves as an important diagnostic molecular marker in ET and PMF. The CALR gene encodes for calreticulin, a multifunctional protein with a C-terminus rich in acidic amino acids and a KDEL ER-retention motif. All the pathologic CALR mutations reported to date are out-of-frame insertion and/or deletions (indel) in exon 9, generating a 1 base-pair (bp) frame shift and a mutant protein with a novel C-terminus rich in basic amino acids and loss of the KDEL ER-retention signal. The most common mutation types are 52-bp deletion (c.1092_1143del, L367fs*46) and 5-bp insertion (c.1154_1155insTTGCC, K385fs*47), and they comprise approximately 85% of CALR mutations in MPN. CALR mutations have been found in hematopoietic stem and progenitor cells in MPN patients and may activate the STAT5 signaling pathway. They are associated with decreased risk of thrombosis in ET and, better survival in PMF compared to JAK2 mutations.

**Useful For:** Rapid and sensitive detection of insertion and deletion-type mutations in exon 9 of CALR. An aid in distinction between reactive thrombocytosis and leukocytosis versus a myeloproliferative neoplasm (MPN), especially essential thrombocythemia (ET) and primary myelofibrosis (PMF), and is highly informative in cases in which JAK2 and MPL testing are negative. Especially helpful to the pathologist in those bone marrow cases with ambiguous etiology of thrombocytosis, equivocal bone marrow morphologic findings of MPN, and unexplained reticulocytosis. An aid in prognostication of...
PMF and thrombosis risk assessment in ET

**Interpretation:** An interpretive report will be issued. The results will be reported as 1 of the 3 states if DNA amplification is successful (see Cautions): -Positive. A deletion/insertion-type mutation was detected in CALR, exon 9. -Negative. No deletion or insertion was detected in CALR, exon 9. -Equivocal. A small amplicon suspicious for a deletion/insertion type mutation was detected in CALR, exon 9. Positive mutation status is highly suggestive of a myeloid neoplasm, but must be correlated with clinical and other laboratory and morphologic features for definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative neoplasm or other neoplastic disorders.

**Reference Values:**
An interpretive report will be provided

**Clinical References:**

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**CALR Mutation Analysis, Myeloproliferative Neoplasm (MPN), Reflex**

**Clinical Information:** The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR-ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide mutation in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). The JAK2 V617F is present in 95% to 98% of polycythemia vera (PV), and 50% to 60% of primary myelofibrosis (PMF) and essential thrombocytemia (ET). It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome. Detection of the JAK2 V617F is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate the absence of MPN. Other important molecular markers in BCR-ABL1-negative MPN include CALR exon 9 mutation (20%-30% of PMF and ET) and MPL exon 10 mutation (5%-10% of PMF and 3%-5% of ET). Mutations in JAK2, CALR, and MPL are essentially mutually exclusive. A CALR mutation is associated with decreased risk of thrombosis in both ET and PMF, and confers a favorable clinical outcome in PMF patients. A triple negative (JAK2 V617F, CALR, and MPL-negative) genotype is considered a high-risk molecular signature in PMF.

**Useful For:** Aiding in the distinction between a reactive cytosis and a chronic myeloproliferative disorder Evaluates for mutations in CALR in an algorithmic process for the MPNR / Myeloproliferative Neoplasm (MPN), JAK2 V617F with reflex to CALR and MPL

**Interpretation:** An interpretation will be provided under the MPNR / Myeloproliferative Neoplasm (MPN), JAK2 V617F with reflex to CALR and MPL.

**Reference Values:**
Only orderable as a reflex. For more information see MPNR / Myeloproliferative Neoplasm (MPN), JAK2 V617F with reflex to CALR and MPL.

An interpretive report will be provided.
Calreticulin ex9mut Immunostain, Technical Component Only

Clinical Information: The detection of calreticulin exon 9 frameshift mutations can assist in the diagnosis and prognostication of myeloproliferative diseases. Although these mutations are heterogeneous, they all result in a protein with a novel 36-amino acid C terminus the anticalreticulin CAL2 clone specifically identifies. Most patients with essential thrombocythemia or primary myelofibrosis not associated with Janus kinase 2 (JAK2) or MPL mutations are associated with CALR exon 9 mutations and primary myelofibrosis patients carrying CALR mutations have a more indolent clinical course.

Useful For: Identifying the presence of calreticulin exon 9 frameshift mutations in myeloproliferative neoplasms

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Calretinin Immunostain, Technical Component Only

Clinical Information: Calretinin is expressed in benign and malignant mesothelial cells, and strongly expressed in Leydig cells of the testis.

Useful For: Marker of mesothelial cells and Leydig cells of the testis

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Canary Feathers, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
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<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
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</tr>
</tbody>
</table>

Reference values apply to all ages.


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Canary Grass, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Cancer Antigen 125 (CA 125), Serum

**Clinical Information:** Cancer antigen 125 (CA 125) is a glycoprotein antigen normally expressed in tissues derived from coelomic epithelia (ovary, fallopian tube, peritoneum, pleura, pericardium, colon, kidney, stomach). Serum CA 125 is elevated in approximately 80% of women with advanced epithelial ovarian cancer, but assay sensitivity is suboptimal in early disease stages. The average reported sensitivities are 50% for stage I and 90% for stage II or greater. Elevated serum CA 125 levels have been reported in individuals with a variety of nonovarian malignancies including cervical, liver, pancreatic, lung, colon, stomach, biliary tract, uterus, fallopian tube, breast, and endometrial carcinomas. Elevated serum CA 125 levels have been reported in individuals with a variety of benign conditions including: cirrhosis, hepatitis, endometriosis, first trimester pregnancy, ovarian cysts, and pelvic inflammatory disease. Elevated levels during the menstrual cycle also have been reported.

**Useful For:** Evaluating patients’ response to ovarian cancer therapy Predicting recurrent ovarian cancer

**Interpretation:** In monitoring studies, elevations of cancer antigen 125 (CA 125) above the reference interval after debulking surgery and chemotherapy indicate that residual disease is likely (>95% accuracy). However, normal levels do not rule-out recurrence. A persistently rising CA 125 value suggests progressive malignant disease and poor therapeutic response. Physiologic half-life of CA 125 is approximately 5 days. In patients with advanced disease who have undergone cytoreductive surgery and are on chemotherapy, a prolonged half-life (>20 days) may be associated with a shortened disease-free survival.

**Reference Values:**
Males: Not applicable
Females: <46 U/mL

**Clinical References:**

Cancer Antigen 15-3 (CA 15-3), Serum

**Clinical Information:** Carcinoma of the breast is the most prevalent form of cancer in women. These tumors often produce mucinous antigens that are large molecular weight glycoproteins with O-linked oligosaccharide chains. Tumor-associated antigens encoded by the human MUC-1 gene are known by several names, including MAM6, milk mucin antigen, cancer antigen (CA) 27.29, and CA 15-3. CA 15-3 assay values are not elevated in most normal individuals and are frequently elevated in sera from breast cancer patients. Nonmammary malignancies in which elevated CA 15-3 assay values have been reported include: lung, colon, pancreas, primary liver, ovary, cervix, and endometrium.

**Useful For:** Managing breast cancer patients when used in conjunction with clinical information and other diagnostic procedures Serial testing can assist in early detection of disease recurrence in previously treated stage II and III breast cancer patients Monitoring response to therapy in metastatic breast cancer patients

**Interpretation:** Increasing and decreasing values show correlation with disease progression and regression, respectively.(1) Increasing cancer antigen 15-3 (CA 15-3) assay values in patients at risk for breast cancer recurrence after primary therapy may be indicative of recurrent disease before it can be detected clinically (2,3) and may be used as an indication that additional tests or procedures should be performed.
Candida albicans (Monilia), IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>6</td>
<td>&gt; 30</td>
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</tr>
</tbody>
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**Reference Values:**

Cannabinoid Screen:
THC (MARIJUANA) Metabolite - Negative; Cutoff: 5 ng/mL
Cannabinoid Confirmation:
Tetrahydrocannabinol (THC)
Carboxy-THC
Hydroxy-THC
Cannabinol
Cannabidiol
Confirmation threshold: 1.0 ng/mL

**CWAY 82493 Caraway, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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</table>

**Clinical Information:** Carbamazepine is an aromatic anticonvulsant. Oxcarbamazine, eslicarbazepine, lamotrigine, phenytoin, fosphenytoin, and phenobarbital are also in this category. Carbamazepine is FDA-approved for the treatment of epilepsy, trigeminal neuralgia, and bipolar disorder. A minority of carbamazepine-treated persons have cutaneous adverse reactions that vary in prevalence and severity, with some forms associated with substantial morbidity and mortality. More severe reactions, such as the hypersensitivity syndrome, are associated with mortality of up to 10% and include symptoms such as rash, fever, eosinophilia, hepatitis, and nephritis. The most severe reactions, such as the Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), are characterized by a blistering rash affecting a variable percentage of the body-surface area. TEN is the rarest of these phenotypes and is associated with mortality of up to 30%. Drug reaction with eosinophilia and systemic symptoms (DRESS) and maculopapular exanthema (MPE) may also be related to carbamazepine exposure. According to the FDA-approved label for carbamazepine, the estimated incidence of SJS-TEN is 1 to 6 cases in 10,000 persons of European ancestry who are exposed to the drug. The rate of SJS-TEN as a result of carbamazepine exposure is about 10 times higher in some Asian countries. Clinical studies have demonstrated associations between some human leukocyte antigen (HLA) genotypes and drug-associated cutaneous adverse reactions. The presence of the HLA-B*15:02 allele varies throughout Asia: 10% to 15% frequency in Chinese; 2% to 4% frequency in Southeast Asians, including Indians; and less than 1% frequency in Japanese and Koreans. This allele is strongly associated with greater risk of SJS and TEN in patients treated with carbamazepine or oxcarbazepine, and has also been associated with SJS/TEN with phenytoin use. There is very limited evidence associating SJS/TEN/DRESS or MPE and other aromatic anticonvulsants in patients who are positive for HLA-B*15:02. The HLA-A*31:01 allele, which has a prevalence of 2% to 5% in Northern European populations, 6% among Hispanic/South American populations, and 8% among Japanese populations, has been significantly associated with greater risk of MPE, DRESS, and SJS/TEN among patients treated with carbamazepine. In the absence of HLA-A*31:01, the risk for drug-associated cutaneous adverse reactions is 3.8%, but in the presence of this allele, the risk increases to 26%. The evidence linking other aromatic anticonvulsants with SJS/TEN in the presence of the HLA-A*31:01 allele is weaker; however, an alternative medication should be chosen with caution. The FDA-approved label for carbamazepine states that the screening of patients in genetically at-risk populations (ie, patients of Asian descent) for the presence of the HLA-B*15:02 allele should be carried out prior to initiating treatment with carbamazepine. The FDA-approved label also notes the association of HLA-A*31:01 allele with drug-associated cutaneous adverse reactions regardless of ethnicity, but does not specifically mandate screening of patients. The FDA-approved label for oxcarbazepine indicates that testing for the presence of the HLA-B*15:02 allele should be considered in patients with ancestry including genetically at-risk populations prior to initiation of therapy. According to the most recent Clinical Pharmacogenetic Implementation Consortium (CPIC) guideline, patients who are HLA-B*15:02 positive should not be prescribed carbamazepine or oxcarbazepine if alternative agents are available; however, caution should be used in selecting an alternative medication as there is weaker evidence that also links other aromatic anticonvulsants with SJS/TEN in patients positive for HLA-B*15:02. Furthermore, phenytoin is the subject of a separate CPIC guideline with recommendations to avoid phenytoin in HLA-B*15:02 positive individuals, along with additional recommendations based on CYP2C9 genotype. Patients who are HLA-A*31:01 positive should not be prescribed carbamazepine if alternative agents are available. However, although very limited evidence links SJS/TEN/DRESS/MPE with other aromatic anticonvulsants, among HLA-A*31:01-positive patients, caution should be used in selecting an alternative medication.

**Useful For:** Identifying individuals with increased risk of risk of carbamazepine- or oxcarbazepine-associated cutaneous adverse reactions

**Interpretation:** The presence of the HLA-B*15:02 and/or HLA-A*31:01 allele confers increased risk for hypersensitivity to carbamazepine. The presence of the HLA-B*15:02 allele also confers increased risk for hypersensitivity to oxcarbazepine and phenytoin. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Carbamazepine Hypersensitivity Pharmacogenomics, Saliva**

**Clinical Information:** Carbamazepine is an aromatic anticonvulsant. Oxcarbazepine, eslicarbazepine, lamotrigine, phenytoin, fosphenytoin, and phenobarbital are also in this category. Carbamazepine is FDA-approved for the treatment of epilepsy, trigeminal neuralgia, and bipolar disorder. A minority of carbamazepine-treated persons have cutaneous adverse reactions that vary in prevalence and severity, with some forms associated with substantial morbidity and mortality. More severe reactions, such as the hypersensitivity syndrome, are associated with mortality of up to 10% and include symptoms such as rash, fever, eosinophilia, hepatitis, and nephritis. The most severe reactions, such as the Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), are characterized by a blistering rash affecting a variable percentage of the body-surface area. TEN is the rarest of these phenotypes and is associated with mortality of up to 30%. Drug reaction with eosinophilia and systemic symptoms (DRESS) and maculopapular exanthema (MPE) may also be related to carbamazepine exposure. According to the FDA-approved label for carbamazepine, the estimated incidence of SJS-TEN is 1 to 6 cases in 10,000 persons of European ancestry who are exposed to the drug. The rate of SJS-TEN as a result of carbamazepine exposure is about 10 times higher in some Asian countries. Clinical studies have demonstrated associations between some human leukocyte antigen (HLA) genotypes and drug-associated cutaneous adverse reactions. The presence of the HLA-B*15:02 allele varies throughout Asia: 10% to 15% frequency in Chinese, 2% to 4% frequency in Southeast Asians, including Indians, and less than 1% frequency in Japanese and Koreans. This allele is strongly associated with greater risk of SJS and TEN in patients treated with carbamazepine or oxcarbazepine, and has also been associated with SJS/TEN with phenytoin use. There is very limited evidence associating SJS/TEN/DRESS or MPE and other aromatic anticonvulsants in patients who are positive for HLA-B*15:02. The HLA-A*31:01 allele, which has a prevalence of 2% to 5% in Northern European populations, 6% among Hispanic/South American populations, and 8% among Japanese populations, has been significantly associated with greater risk of MPE, DRESS, and SJS/TEN among patients treated with carbamazepine. In the absence of HLA-A*31:01, the risk for drug-associated cutaneous adverse reactions is 3.8%, but in the presence of this allele, the risk increases to 26%. The evidence linking other aromatic anticonvulsants with SJS/TEN in the presence of the HLA-A*31:01 allele is weaker; however, an alternative medication should be chosen with caution. The FDA-approved label for carbamazepine states that the screening of patients in genetically at-risk populations (ie, patients of Asian descent) for the presence of the HLA-B*15:02 allele should be carried out prior to initiating treatment with carbamazepine. The FDA-approved label also notes the association of HLA-A*31:01 allele with drug-associated cutaneous adverse reactions regardless of ethnicity but does not specifically mandate screening of patients. The FDA-approved label for oxcarbazepine indicates that testing for the presence of the HLA-B*15:02 allele should be considered in patients with ancestry including genetically at-risk populations prior to initiation of therapy. According to the most recent Clinical Pharmacogenetic Implementation Consortium (CPIC) guideline, patients who are HLA-B*15:02 positive should not be prescribed carbamazepine or oxcarbazepine if alternative agents are available; however, caution should be used in selecting an alternative medication as there is weaker evidence that also links other aromatic anticonvulsants with SJS/TEN in patients positive for HLA-B*15:02. Furthermore, phenytoin is the subject of a separate CPIC guideline with recommendations to avoid phenytoin in HLA-B*15:02 positive individuals, along with additional recommendations based on CYP2C9 genotype. Patients who are HLA-A*31:01 positive should not be
prescribed carbamazepine if alternative agents are available. However, although very limited evidence links SJS/TEN/DRESS/MPE with other aromatic anticonvulsants among HLA-A*31:01-positive patients, caution should be used in selecting an alternative medication.

**Useful For:** Identifying individuals with increased risk of carbamazepine- or oxcarbazepine-associated cutaneous adverse reactions Genotyping patients who prefer not to have their blood drawn

**Interpretation:** The presence of the HLA-B*15:02 and/or HLA-A*31:01 allele confers increased risk for hypersensitivity to carbamazepine. The presence of the HLA-B*15:02 allele also confers increased risk for hypersensitivity to oxcarbazepine. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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Carbamazepine Profile, Serum

**Clinical Information:** Carbamazepine is a common antiepileptic drug. It is a first-line drug for treatment of partial seizures and trigeminal neuralgia. Carbamazepine is metabolized by the liver to carbamazepine-10,11-epoxide (CBZ10-11), which is pharmacologically active and potentially toxic. CBZ10-11 is, in turn, inactivated by hepatic conversion to a transdiol derivative. CBZ10-11 may be responsible for the congenital abnormalities that are sometimes associated with the use of carbamazepine during early pregnancy. There have been cases of severe seizures exacerbation when serum epoxide levels were increased. Toxic levels of CBZ10-11 can occur during: -Concomitant administration of other drugs that induce hepatic oxidizing enzymes (eg, most antiepileptic drugs [with the exception of valproic acid and the benzodiazepines], propoxyphene) -Concomitant administration of drugs that inhibit its breakdown such as valproic acid, felbamate, and lamotrigine -High-dose carbamazepine therapy, especially in combination with the above conditions

**Useful For:** Monitoring patients exhibiting symptoms of carbamazepine toxicity whose total serum carbamazepine concentration is within the therapeutic range, but who may be producing significant levels of the active metabolite epoxide Free carbamazepine concentration may also be useful to monitor in patients with altered or unpredictable protein binding capacity

**Interpretation:** The clinically acceptable serum concentration of carbamazepine-10,11-epoxide (CBZ10-11) is not well established, but 4.0 mcg/mL has often been used as an upper limit for its therapeutic range. The ratio of CBZ10-11 to carbamazepine is usually less than or equal to 0.2 mcg/mL in symptomatic adults and less than or equal to 0.3 mcg/mL in children. Clinical correlation is aided by comparing values obtained when the patient is symptomatic with those obtained when the patient has improved.

**Reference Values:**

<table>
<thead>
<tr>
<th>CARBAMAZEPINE, TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic: 4.0-12.0 mcg/mL</td>
</tr>
<tr>
<td>Critical value: &gt; or =15.0 mcg/mL</td>
</tr>
</tbody>
</table>
Carbamazepine, Free and Total, Serum

**Clinical Information:** Carbamazepine (Tegretol) is an effective treatment for complex partial seizures, with or without generalization to tonic-clonic seizures. It is frequently administered in conjunction with other antiepileptic agents, such as phenytoin and valproic acid. Under normal circumstances, the carbamazepine that circulates in blood is 75% protein bound. In severe uremia, carbamazepine may be displaced from protein, resulting in a higher free (unbound) fraction of the drug circulating in blood. Since neurologic activity and toxicity are directly related to the circulating free fraction of drug, adjustment of dosage based on knowledge of the free carbamazepine level may be useful in patients with severe uremia.

**Useful For:** Monitoring carbamazepine (free and total) therapy in uremic patients

**Interpretation:** In patients with normal renal function, optimal response is often associated with free (unbound) carbamazepine levels greater than 1.0 mcg/mL, and toxicity may occur when the free carbamazepine is greater than or equal to 4.0 mcg/mL. In uremic patients, the free carbamazepine level may be a more useful guide for dosage adjustments than the total level. In patients with severe uremia, subtherapeutic total carbamazepine levels in the range of 1.0 to 2.0 mcg/mL may be associated with therapeutic free levels. Toxicity may occur in these patients when the free carbamazepine level is greater than or equal to 4.0 mcg/mL (even though the total carbamazepine concentration is <15.0 mcg/mL). As with the serum levels of other anticonvulsant drugs, total and free carbamazepine levels should be correlated with the patient's clinical condition. They are best used as a guide in dose adjustment.

**Reference Values:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARBAMAZEPINE, TOTAL</td>
<td>Therapeutic: 4.0-12.0 mcg/mL</td>
</tr>
<tr>
<td></td>
<td>Critical value: &gt; or =15.0 mcg/mL</td>
</tr>
<tr>
<td>CARBAMAZEPINE, FREE</td>
<td>Therapeutic: 1.0-3.0 mcg/mL</td>
</tr>
<tr>
<td></td>
<td>Critical value: &gt; or =4.0 mcg/mL</td>
</tr>
</tbody>
</table>

**Clinical References:**

1. Svinarov DA, Pippenger CE: Relationships between carbamazepine-diol, carbamazepine-epoxide, and carbamazepine total and free steady-state concentrations in epileptic patients: the influence of age, sex, and comedication. Ther Drug Monit 1996;18:660-665
3. Dasgupta A, Volk A: Displacement of valproic acid and

**Carbamazepine, Free, Serum**

**Clinical Information:** Carbamazepine (Tegretol) is an effective treatment for complex partial seizures, with or without generalization to tonic-clonic seizures. It is frequently administered in conjunction with other antiepileptic agents, such as phenytoin and valproic acid. Under normal circumstances, the carbamazepine that circulates in blood is 70% to 80% protein-bound. Only the free drug is able to enter the interstitial space in the brain where the pharmacological effects occur. Patient management is best guided by monitoring free serum concentrations when protein binding is altered. Altered protein binding occurs in patients with hypoalbuminemia observed during pregnancy, in the malnourished, and liver disease. In patients with renal disease, uremia may develop whose byproducts can displace bound carbamazepine increasing the unbound fraction. Administration of drugs that are able to compete for serum protein binding sites may also increase the unbound fraction of carbamazepine. Since neurologic activity and toxicity of carbamazepine are directly related to the circulating free fraction of drug, adjustment of dosage based on knowledge of the free carbamazepine concentration may be more useful in these patient populations.

**Useful For:** Monitoring unbound or free carbamazepine levels in patients where the total carbamazepine result is within the therapeutic range but the patient is experiencing side effects

Monitoring carbamazepine (free) therapy in uremic patients

**Interpretation:** In patients with normal renal function, optimal response is often associated with free (unbound) carbamazepine levels above 1.0 mcg/mL, and toxicity may occur when the free carbamazepine is greater than or equal to 4.0 mcg/mL. Under normal circumstances, the carbamazepine that circulates in blood is 75% protein-bound. Therapies or conditions such as uremia that displace carbamazepine from protein cause a higher free (unbound) fraction of the drug circulating in blood. In uremia, the free carbamazepine level may be a more useful guide for dosage adjustments than the total level. In patients with severe uremia, subtherapeutic total carbamazepine levels in the range of 1.0 to 2.0 mcg/mL may be associated with therapeutic free carbamazepine levels. Toxicity may occur when the free carbamazepine level is greater than or equal to 4.0 mcg/mL (even though the total carbamazepine concentration is <15.0 mcg/mL). As with the serum levels of other anticonvulsant drugs, total and free carbamazepine levels should be correlated with the patient's clinical condition. Serum levels are best used as a guide in dose adjustment.

**Reference Values:**

Therapeutic concentration: 1.0-3.0 mcg/mL

Critical value: > or =4.0 mcg/mL

**Carbamazepine, Total, Serum**

**Clinical Information:** Carbamazepine (Tegretol) is used in the control of partial seizures with both temporal lobe and psychomotor symptoms, and for generalized tonic-clonic seizures. It is also used for analgesia in trigeminal neuralgia. Carbamazepine exhibits a volume of distribution of 1.4 L/kg with an elimination half-life of 15 hours. Protein binding averages 70%. Carbamazepine-10,11-epoxide (CBZ10-11) is an active metabolite that represents the predominant form of the drug in children. The volume of distribution of CBZ10-11 is 1.1 L/kg, and the half-life is 5-8 hours. Aplastic anemia and agranulocytosis are rare side effects of treatment with carbamazepine; baseline hematologic data should be documented before treatment is initiated. Toxicity associated with carbamazepine overdose occurs when the blood level is 15.0 mcg/mL or higher and is typified by irregular breathing, muscle irritability, and hyperreflexia; followed by hyporeflexia, tachycardia, hypotension, and impaired consciousness with coma in severe toxicity. The higher the blood level, the more severe the symptoms.

**Useful For:** Monitoring therapy, Determining compliance, Assessing toxicity

**Interpretation:** Dosage adjustments are usually guided by monitoring blood levels. Most patients respond well when the serum concentration is in the range of 4.0 to 12.0 mcg/mL. Toxicity often occurs when levels are greater than or equal to 15.0 mcg/mL.

**Reference Values:**
- Therapeutic: 4.0-12.0 mcg/mL
- Critical value: > or =15.0 mcg/mL

**Clinical References:**

**Carbamazepine-10,11-Epoxide, Serum**

**Clinical Information:** Carbamazepine is a common antiepileptic drug. It is a first-line drug for treatment of partial seizures and trigeminal neuralgia. Carbamazepine is metabolized by the liver to carbamazepine-10,11-epoxide (CBZ10-11) which is pharmacologically active and potentially toxic. CBZ10-11 is, in turn, inactivated by hepatic conversion to a transdiol derivative. CBZ10-11 may be responsible for the congenital abnormalities that are sometimes associated with the use of carbamazepine during early pregnancy. There have been cases of severe seizures exacerbation when serum epoxide levels were increased. Toxic levels of CBZ10-11 can occur during: -Concomitant administration of other drugs that induce hepatic oxidizing enzymes (eg, most antiepileptic drugs [with the exception of valproic acid and the benzodiazepines], propoxyphene) -Concomitant administration of drugs that inhibit its breakdown such as valproic acid, felbamate, and lamotrigine -High-dose carbamazepine therapy, especially in combination with the above conditions

**Useful For:** Monitoring patients exhibiting symptoms of carbamazepine toxicity whose total serum carbamazepine concentration is within the therapeutic range, but who may be producing significant levels of the active metabolite epoxide, which can accumulate to concentrations equivalent to carbamazepine

**Interpretation:** The clinically acceptable serum concentration of carbamazepine-10,11-epoxide (CBZ10-11) is not well established, but 4.0 mcg/mL has often been used as an upper limit for its therapeutic range. The ratio of CBZ10-11 to carbamazepine is usually < or =0.2 mcg/mL in symptomatic adults and < or =0.3 mcg/mL in children. Clinical correlation is aided by comparing values obtained when the patient is symptomatic with those obtained when the patient has improved.

**Reference Values:**
- CARBAMAZEPINE, TOTAL
  - Therapeutic: 4.0-12.0 mcg/mL
Critical value: > or =15.0 mcg/mL

CARBAMAZEPINE-10,11-EPOXIDE
Therapeutic concentration: 0.4-4.0 mcg/mL
Toxic concentration: > or =8.0 mcg/mL

Clinical References:

Carbapenemase Detection-Carba NP Test
Clinical Information: Gram-negative bacilli (GNB) with acquired carbapenemases have disseminated worldwide, rendering them a global threat. The therapeutic armamentarium for infections caused by carbapenem-resistant Enterobacteriaceae (CRE) is limited, and CRE infections have been associated with significant mortality. Enterobacteriaceae harboring Klebsiella pneumoniae carbapenemase are endemic in some regions of the United States, and although still sporadic, GNB harboring New Delhi metallo-beta-lactamase have been reported from several states. Timely detection of these carbapenemases (along with emerging carbapenemases such as OXA-48 and VIM) is important. Detection is challenging since isolates may have only borderline reductions in susceptibility to carbapenems, and carbapenem resistance may be mediated by mechanisms other than carbapenemases (eg, AmpC or extended-spectrum beta-lactamase with decreased membrane permeability). While molecular methods are confirmatory, testing may not be immediately available and may be limited by the number of targets assayed. The modified Hodge test suffers from lack of specificity, a long turnaround time, and poor sensitivity for metallo-beta-lactamase detection. The Carba NP test is preferred over the modified Hodge test due to improved specificity and faster turnaround time. The Carba NP test is more specific than and as sensitive as the carbapenemase-modified Hodge test. If an isolate is suspected to possess KPC or NDM carbapenemase (eg, due to local epidemiology), KPC and NDM PCR (KPNRP / KPC (blaKPC) and NDM (blaNDM) in Gram-Negative Bacilli, Molecular Detection, PCR) may be preferred over the Carba NP test.

Useful For: Confirmation of carbapenemase production from pure isolates of Enterobacteriaceae or Pseudomonas aeruginosa

Interpretation: A positive result indicates production of a carbapenemase by the isolate submitted for testing. A negative result indicates lack of production of a carbapenemase by the isolate submitted for testing.

Reference Values: Negative

Clinical References:

Carbapenemase Detection-Carba NP Test (Bill Only)
Reference Values: This test is for billing purposes only.
Carbohydrate Antigen 19-9 (CA 19-9), Pancreatic Cyst Fluid

Clinical Information: Carbohydrate antigen 19-9 (CA 19-9) is a modified Lewis(a) blood group antigen, and has been used as a tumor marker. Serum CA 19-9 concentrations may be elevated in patients with gastrointestinal malignancies such as cholangiocarcinoma, colon cancer, or pancreatic cancer. While serum CA 19-9 is neither sensitive nor specific for pancreatic cancer, concentrations of CA 19-9 in pancreatic cyst fluid may help determine whether a pancreatic cyst is benign. Cystic lesions of the pancreas are of various types: -Benign cysts: - Inflammatory cysts (pseudocysts) - Serous cysts (serous cystadenoma) - Mucinous cysts: - Premalignant (mucinous cystadenoma) - Malignant (cystadenocarcinoma, intrapapillary mucinous neoplasia) Pancreatic cyst fluid CA 19-9 results should be used in conjunction with imaging studies, cytology, and other cyst-fluid tumor markers, such as carcinoembryonic antigen and amylase.

Useful For: As an adjunct in the assessment of pancreatic cysts, when used in conjunction with carcinoembryonic antigen, amylase, imaging studies and cytology

Interpretation: Cyst fluid carbohydrate antigen 19-9 (CA19-9) concentrations < or =37 U/mL indicate a low risk for a mucinous cyst, and are more consistent with serous cystadenoma or pseudocyst. The sensitivity and specificity are approximately 19% and 98%, respectively, at this concentration. Correlation of these test results with cytology and imaging is recommended.

Reference Values: An interpretive report will be provided.


Carbohydrate Antigen 19-9 (CA 19-9), Peritoneal Fluid

Clinical Information: Malignancy accounts for approximately 7% of cases of ascites formation. Malignant disease can cause ascites by various mechanisms including: peritoneal carcinomatosis (53%), massive liver metastasis causing portal hypertension (13%), peritoneal carcinomatosis plus massive liver metastasis (13%), hepatocellular carcinoma plus cirrhosis (7%), and chylous ascites due to lymphoma (7%). The evaluation and diagnosis of malignancy-related ascites is based on the patient clinical history, ascites fluid analysis, and imaging tests. The overall sensitivity of cytology for the detection of malignancy-related ascites ranges from 58% to 75%. Cytology examination is most successful in patients with ascites related to peritoneal carcinomatosis as viable malignant cells are exfoliated into the ascitic fluid. However, only approximately 53% of patients with malignancy-related ascites have peritoneal carcinomatosis. Patients with other causes of malignancy-related ascites almost always have a negative cytology. Carbohydrate antigen 19-9 (CA 19-9) is a modified Lewis(a) blood group antigen. CA 19-9 may be elevated in the serum patients with gastrointestinal malignancies such as cholangiocarcinoma, pancreatic cancer, or colon cancer. Measurement of CA 19-9 in ascitic fluid is sometimes used in combination with cytology for detecting malignancy-related ascites.

Useful For: An adjunct to cytology to differentiate between malignancy-related ascites and benign causes of ascites formation

Interpretation: A peritoneal fluid carbohydrate antigen 19-9 (CA 19-9) concentration >32 U/mL is suspicious, but not diagnostic, of a malignancy-related ascites. This clinical decision limit cutoff yielded 44% sensitivity and 93% specificity in a study of 137 patients presenting with ascites. However, ascites caused by malignancies not associated with increase serum CA 19-9 concentrations, including
lymphoma, mesothelioma, leukemia, and melanoma, routinely had CA 19-9 concentrations <32 U/mL. Therefore, negative results should be interpreted with caution, especially in patients who have or are suspected of having a malignancy not associated with elevated CA 19-9 levels in serum.

**Reference Values:**
An interpretive report will be provided.


**Carbohydrate Antigen 19-9 (CA 19-9), Pleural Fluid**

**Clinical Information:** Pleural effusions occur as a consequence of either nonmalignant conditions (including congestive heart failure, pneumonia, pulmonary embolism, and liver cirrhosis) or malignant conditions (including lung, breast, and lymphoma cancers). Diagnosing the cause of an effusion can be difficult, requiring cytological examination of the fluid. Analysis of various tumor markers in pleural fluid has shown that these markers can differentiate between effusions caused by nonmalignant and malignant conditions and can enhance cytology findings. Carbohydrate antigen 19-9 (CA 19-9) is a modified Lewis(a) blood group antigen. Healthy adults typically produce low to undetectable levels of CA 19-9. Serum concentrations of CA 19-9 may be elevated in patients with certain malignancies that secrete CA 19-9 into circulation, including cholangiocarcinoma, colorectal, stomach, bile duct, lung, ovarian, and pancreatic cancers. Pleural fluid concentrations of CA 19-9 have been reported to be elevated in patients with certain malignancies. Malignancies that can secrete CA 19-9 and elevate serum CA 19-9 concentrations, including cholangiocarcinoma, colorectal, stomach, bile duct, lung, ovarian, and pancreatic cancers, typically also elevate CA 19-9 in pleural fluid. In contrast, malignancies that do not secrete CA 19-9, including mesothelioma, lymphoma, leukemia, and melanoma, have low concentrations of CA 19-9 in pleural fluid comparable to concentrations observed in nonmalignant effusions. CA 19-9 results should be used in conjunction with cytological analysis of pleural fluid, imaging studies, and other clinical findings.

**Useful For:** An adjuvant to cytology and imaging studies to differentiate between nonmalignant and malignant causes of pleural effusions

**Interpretation:** A pleural fluid carbohydrate antigen 19-9 (CA 19-9) concentration of 20.0 U/mL or higher is suspicious, but not diagnostic, of a malignant source of the effusion. This cutoff yielded a sensitivity of 35%, specificity of 95%, and positive predictive value of 88% in a study of 200 patients presenting with effusion. CA 19-9 concentrations were significantly higher in effusions caused by CA 19-9-secreting malignancies, including cholangiocarcinoma, colorectal, stomach, bile duct, lung, ovarian, and pancreatic cancers. However, effusions caused by non-CA 19-9-secreting malignancies, including lymphoma, mesothelioma, leukemia, and melanoma, routinely had CA 19-9 concentrations below 20.0 U/mL. Therefore, negative results should be interpreted with caution, especially in patients who have or are suspected of having a non-CA 19-9-secreting malignancy. Correlation of all tumor marker results with cytology and imaging is highly recommended.

**Reference Values:**
An interpretive report will be provided.

**Carbohydrate Antigen 19-9 (CA 19-9), Serum**

**Clinical Information:** Carbohydrate antigen 19-9 (CA 19-9) is a modified Lewis(a) blood group antigen. CA 19-9 may be elevated in patients with gastrointestinal malignancies such as cholangiocarcinoma, pancreatic cancer, or colon cancer. Benign conditions such as cirrhosis, cholestasis, and pancreatitis also result in elevated serum CA 19-9 concentrations but in these cases values usually are below 1,000 U/mL. Individuals that are Lewis negative (5%-7% of the population) do not express CA 19-9 due to the lack of the enzyme fucosyltransferase needed for CA 19-9 production. In these individuals, a low or undetectable serum CA 19-9 concentration is not informative regarding cancer recurrence.

**Useful For:** Potentially useful adjunct for diagnosis and monitoring of pancreatic cancer May be used for differentiating patients with cholangiocarcinoma and primary sclerosing cholangitis (PSC) from those with PSC alone

**Interpretation:** Serial monitoring of carbohydrate antigen 19-9 (CA 19-9) should begin prior to therapy to verify post-therapy decreases in CA 19-9 and to establish a baseline for evaluating possible recurrence. Single values of CA 19-9 are less informative. Elevated values may be caused by a variety of malignant and nonmalignant conditions including cholangiocarcinoma, pancreatic cancer, and/or colon cancer.

**Reference Values:**
<35 U/mL

**Clinical References:** Torok N, Gores GJ: Cholangiocarcinoma. Semin Gastrointest Dis 2001 Apr;12(2):125-132

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**Carbohydrate Deficient Transferrin for Congenital Disorders of Glycosylation, Serum**

**Clinical Information:** Congenital disorders of glycosylation (CDG), formerly known as carbohydrate-deficient glycoprotein syndrome, are a group of over 100 inherited metabolic disorders affecting several steps of the pathway involved in the glycosylation of proteins. CDG are currently classified into 2 main groups. Type I CDG is characterized by defects in the assembly or transfer of the dolichol-linked glycan, while type II involves processing defects of the glycan. Apolipoprotein CIII (Apo-CIII) isoforms, a protein with a single core 1 mucin type O-glycosylate protein, is a complementary evaluation for the CDG type II profile. This analysis will evaluate mucin type O-glycosylation, a defect that happens in the Golgi apparatus, and will change the ratios, increasing the asialo or monoisalio forms and decreasing the fully sialilate (disialo) forms. CDG typically present as multi-systemic disorders with a broad clinical spectrum including, but not limited to, developmental delay, hypotonia, with or without neurological abnormalities, abnormal magnetic resonance imaging findings, skin manifestations, and coagulopathy. There is considerable variation in the severity of this group of diseases ranging from a mild presentation in adults to severe multi-organ dysfunctions causing infantile lethality. In some subtypes, MPI-CDG (CDG-Ib) in particular, intelligence is not compromised. CDG should be suspected in all patients with neurological abnormalities including developmental delay and seizures, brain abnormalities such as cerebellar atrophy or hypoplasia as well as unexplained liver dysfunction. Abnormal subcutaneous fat distribution and chronic diarrhea each may or may not be present. The differential diagnosis of abnormal transferrin patterns also includes liver disease not related to CDG including galactosemia, hereditary fructose intolerance in acute crisis, and liver disease of unexplained etiology. Transferrin and apolipoprotein CIII isoform analysis test is the initial screening test for CDG. The results of the transferrin and apolipoprotein CIII isoform analysis should be correlated with the clinical presentation to determine the most appropriate follow-up testing strategy including enzyme, molecular, and research-based testing. Enzymatic analysis for phosphomannomutase and phosphomannose isomerase in leukocytes (PMMIL / Phosphomannomutase [PMM] and Phosphomannose Isomerase [PMI], Leukocytes) should be performed if either PMM2-CDG (CDG-Ia) or MPI-CDG (CDG-Ib) are suspected.

**Useful For:** Screening for congenital disorders of glycosylation
**Interpretation:** Positive test results could be due to a genetic or nongenetic condition; additional confirmatory testing is required. Results are reported as the mono-oligosaccharide/di-oligosaccharide transferrin ratio, the a-oligosaccharide/di-oligosaccharide transferrin ratio, and the tri-sialo/di-oligosaccharide transferrin ratio, the apolipoprotein CIII-I/apolipoprotein CIII-2 ratio, and the apolipoprotein CIII-0/apolipoprotein CIII-2 ratio. The report will include the quantitative results and an interpretation. The congenital disorders of glycosylation (CDG) profiles are categorized in 4 types: -CDG type I profile. Mono-oligosaccharide/di-oligosaccharide transferrin ratio and/or the a-oligosaccharide/di-oligosaccharide transferrin ratio are abnormal. This group should have the apolipoprotein C-III profile within the normal ranges, because the Golgi system is not affected in CDG type I. -CDG type II profile. The tri-sialo/di-oligosaccharide transferrin ratio is abnormal. In this category, the apolipoprotein C-III profile will have 2 scenarios: -The apolipoprotein CIII-I/apolipoprotein CIII-2 ratio and/or the apolipoprotein CIII-0/apolipoprotein CIII-2 ratio will be abnormal when the defect is most likely glycan processing in the Golgi apparatus, therefore the CDG defect is likely. -The apolipoprotein CIII-I/apolipoprotein CIII-2 ratio and/or the apolipoprotein CIII-0/apolipoprotein CIII-2 ratio are normal, in this case most likely the defects do not involve the Golgi system, thus the molecular defect is different. -CDG mixed type profile (type I and II together). In this type of profile one can have abnormal tri-sialo/di-oligosaccharide transferrin ratio with the mono-oligosaccharide/di-oligosaccharide transferrin ratio and/or the a-oligosaccharide/di-oligosaccharide transferrin ratio abnormal, and may have the apolipoprotein CIII-I/apolipoprotein CIII-2 ratio and the apolipoprotein CIII-0/apolipoprotein CIII-2 ratio normal or abnormal, depending if the defects involve Golgi apparatus. When the profile cannot be categorized following the above classification, all the abnormal transferrin and/or Apo-CIII species will be reported descriptively according to the molecular mass stating the possible structures. Reports of abnormal results will include recommendations for additional biochemical and molecular genetic studies to more precisely identify the correct form of CDG. Treatment options, the name and telephone number of contacts who may provide studies at Mayo Clinic or elsewhere, and a telephone number for one of the laboratory directors (if the referring physician has additional questions) will be provided.

**Reference Values:**

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Normal</th>
<th>Indeterminate</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transferrin Mono-oligo/Di-oligo Ratio</td>
<td>&lt; or =0.06</td>
<td>0.07-0.09</td>
<td>&gt; or =0.10</td>
</tr>
<tr>
<td>Transferrin A-oligo/Di-oligo Ratio</td>
<td>&lt; or =0.011</td>
<td>0.012-0.021</td>
<td>&gt; or =0.022</td>
</tr>
<tr>
<td>Transferrin Tri-sialo/Di-oligo Ratio</td>
<td>&lt; or =0.05</td>
<td>0.06-0.12</td>
<td>&gt; or =0.13</td>
</tr>
<tr>
<td>Apo CIII-I/Apo CIII-2 Ratio</td>
<td>&lt; or =2.91</td>
<td>2.92-3.68</td>
<td>&gt; or =3.69</td>
</tr>
<tr>
<td>Apo CIII-0/Apo CIII-2 Ratio</td>
<td>&lt; or =0.48</td>
<td>0.49-0.68</td>
<td>&gt; or =0.69</td>
</tr>
</tbody>
</table>

abnormal CDT levels, which include congenital disorders of glycosylation and other genetic and nongenetic causes of acute or chronic liver disease. CDT testing alone is not recommended for general screening for alcoholism; however, when combined with other methods (ie, gamma-glutamyltransferase, mean corpuscular volume, patient self-reporting, ethylglucuronide analysis), clinicians can expect to identify the majority of patients who consume a large amount of alcohol.

**Useful For:** An indicator of chronic alcohol abuse

**Interpretation:** Patients with chronic alcoholism may develop abnormally glycosylated transferrin isoforms (ie, carbohydrate deficient transferring: CDT >0.12). CDT results from 0.11 to 0.12 are considered indeterminate. Patients with liver disease due to genetic or nongenetic causes may also have abnormal results.

**Reference Values:**
- < or =0.10
- 0.11-0.12 (indeterminate)

**Clinical References:**

---

**Carbohydrate, Urine**

**Clinical Information:** Saccharides (also called carbohydrates) are a group of mono-, di-, and oligosaccharides of endogenous and exogenous sources. Their presence frequently reflects dietary consumption, but can indicate specific pathology if either a particular saccharide or a particular excretory pattern is present. Most saccharides (except glucose) have low renal thresholds and are readily excreted in the urine. The presence of saccharides in urine is seen in some inborn errors of metabolism. Urine tests for reducing substances (eg, copper reduction test) are often used to screen for those disorders. However, in addition to sugars, a number of other substances present in biological fluids (eg, salicylates, uric acid, hippuric acid, ascorbic acid) have reducing properties. Conversely, some saccharides such as sucrose and trehalose do not have reducing properties. Other saccharides present at low concentrations may not be identified by reducing tests. Substances in urine may inhibit glucose oxidase-based tests and, also, other saccharides of diagnostic importance may be present along with glucose in urine. Chromatography of urinary saccharides is, therefore, required in many instances to identify the particular species of saccharide present. Any specimen tested for urinary carbohydrates is concurrently tested for the presence of succinyl nucleosides to screen for inborn errors of purine synthesis.

**Useful For:** Screening for disorders with increased excretion of fructose, glucose, galactose, disaccharides, oligosaccharides, and succinylpurines

**Interpretation:** An interpretive comment is provided that includes the name of the identified saccharide and the probable source.

**Reference Values:**
Negative
- If positive, carbohydrate is identified.

**Clinical References:**
**COHBB 8649**

**Carbon Monoxide, Blood**

**Clinical Information:** Carbon monoxide (CO) poisoning causes anoxia, because CO binds to hemoglobin with an affinity 240 times greater than that of oxygen, thus preventing delivery of oxygen to the tissues. Twenty percent saturation of hemoglobin induces symptoms (headache, fatigue, dizziness, confusion, nausea, vomiting, increased pulse, and respiratory rate). Sixty percent saturation is usually fatal. This concentration is reached when there is 1 part CO per 1,000 parts air. Carboxyhemoglobin diminishes at a rate of about 15% per hour when the patient is removed from the contaminated environment. The most common cause of CO toxicity is exposure to automobile exhaust fumes. Significant levels of carboxyhemoglobin can also be observed in heavy smokers. Victims of fires often show elevated levels from inhaling CO generated during combustion. Susceptibility to CO poisoning is increased in anemic persons.

**Useful For:** Verifying carbon monoxide toxicity in cases of suspected exposure

**Interpretation:** The toxic effects of carbon monoxide can be seen above 20% carboxyhemoglobin. It must be emphasized that the carboxyhemoglobin concentration, although helpful in diagnosis, does not always correlate with the clinical findings or prognosis. Factors other than carboxyhemoglobin concentration that contribute to toxicity include length of exposure, metabolic activity, and underlying disease, especially cardiac or cerebrovascular disease. Moreover, low carboxyhemoglobin concentrations relative to the severity of poisoning may be observed if the patient was removed from the carbon monoxide-contaminated environment a significant amount of time before blood sampling.

**Reference Values:**
- Normal Concentration
  - Non-Smokers: 0-2%
  - Smokers: < or =9%
- Toxic concentration: > or =20%

**Clinical References:**

**THCX 62743**

**Carboxy-Tetrahydrocannabinol (THC) Confirmation, Chain of Custody, Urine**

**Clinical Information:** Delta-9-tetrahydrocannabinol is the active agent of the popularly abused street drug, marijuana. Following consumption of the drug, either by inhalation or ingestion, it is metabolized to a variety of inactive chemicals, 1 of them being delta-9-tetrahydrocannabinol carboxylic acid. The immunochemical procedure used to screen for tetrahydrocannabinol (THC) as part of IDOAU / Drug Abuse Survey, Urine is designed to cross-react with THC carboxylic acid. In almost all medico-legal cases and in screening of employees, or when the patient adamantly denies THC use and the immunochemical test is positive, confirmation of the result by gas chromatography-mass spectrometry and EIA are required. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection and confirmation of drug abuse involving delta-9-tetrahydrocannabinol (marijuana) Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was
under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** The presence of tetrahydrocannabinol carboxylic acid (THC-COOH), a major metabolite of delta-9-tetrahydrocannabinol, in urine at concentrations >15 ng/mL is a strong indicator that the patient has used marijuana. The metabolite of marijuana (THC-COOH) has a long half-life and can be detected in urine for more than 7 days after a single use. The presence of THC-COOH in urine >100 ng/mL indicates relatively recent use, probably within the past 7 days. Levels >500 ng/mL suggest chronic and recent use. Chronic use causes accumulation of THC and THC-COOH in adipose tissue such that it is excreted into the urine for as long as 30 to 60 days from the time chronic use is halted.

**Reference Values:**

Negative
Positives are reported with a quantitative GC-MS result.

Cutoff concentrations:

**IMMUNOASSAY SCREEN**

<50 ng/mL

**THC CARBOXYLIC ACID BY GC-MS**

<3 ng/mL


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**THCU 8898**

**Carboxy-Tetrahydrocannabinol (THC) Confirmation, Urine**

**Clinical Information:** Delta-9-tetrahydrocannabinol is the active agent of the popularly abused street drug, marijuana. Following consumption of the drug, either by inhalation or ingestion, it is metabolized to a variety of inactive chemicals, one of them being delta-9-tetrahydrocannabinol carboxylic acid. The immunochemical procedure used to screen for tetrahydrocannabinol (THC) as part of IDOAU / Drug Abuse Survey, Urine is designed to cross-react with THC carboxylic acid. In almost all medico-legal cases and in screening of employees, or when the patient adamantly denies THC use and the immunochemical test is positive, confirmation of the result by gas chromatography-mass spectrometry (GC-MS) and EIA are required.

**Useful For:** Detection and confirmation of drug abuse involving delta-9-tetrahydrocannabinol (marijuana)

**Interpretation:** The presence of tetrahydrocannabinol carboxylic acid (THC-COOH), a major metabolite of delta-9-tetrahydrocannabinol, in urine at concentrations >15.0 ng/mL is a strong indicator that the patient has used marijuana. The metabolite of marijuana (THC-COOH) has a long half-life and can be detected in urine for more than 7 days after a single use. The presence of THC-COOH in urine >100.0 ng/mL indicates relatively recent use, probably within the past 7 days. Levels >500.0 ng/mL suggest chronic and recent use. Chronic use causes accumulation of THC and THC-COOH in adipose tissue such that it is excreted into the urine for as long as 30 to 60 days from the time chronic use is halted.

**Reference Values:**

Negative

Cutoff concentration:

**Carboxy-THC- by GC/MS**<3.0 ng/mL


Current as of October 11, 2018 2:20 pm CDT   800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Carcinoembryonic Antigen (CEA), Pancreatic Cyst Fluid

**Clinical Information:** Cystic lesions of the pancreas are of various types including: - Benign cysts - Inflammatory cysts (pseudocysts) - Serous cysts (serous cystadenoma) - Mucinous cysts: - Premalignant (mucinous cystadenoma) - Malignant (cystadenocarcinoma, intrapapillary mucinous neoplasia)

The diagnosis of pancreatic cyst type is often difficult and may require correlating imaging studies with results of cytologic examination and tumor marker testing performed on cyst aspirates. Various tumor markers have been evaluated to distinguish nonmucinous, nonmalignant pancreatic cysts from mucinous cysts, which have a high likelihood of malignancy. Carcinoembryonic antigen (CEA) has been found to be the most reliable tumor marker for identifying those pancreatic cysts that are likely mucinous. In cyst aspirates, CEA concentrations of 200 ng/mL and above are highly suspicious for mucinous cysts. The greater the CEA concentration, the greater the likelihood that the mucinous cyst is malignant. However, CEA testing does not reliably distinguish between benign, premalignant, or malignant mucinous cysts. CEA test results should be correlated with the results of imaging studies, cytology, other cyst fluid tumor markers (ie, amylase and CA 19-9), and clinical findings for diagnosis.

**Useful For:** When used in conjunction with imaging studies, cytology, and other pancreatic cyst fluid tumor markers: - Distinguishing between mucinous and nonmucinous pancreatic cysts - Determining the likely type of malignant pancreatic cyst

**Interpretation:** A pancreatic cyst fluid carcinoembryonic antigen (CEA) concentration of 200 ng/mL and higher is very suggestive for a mucinous cyst but is not diagnostic. The sensitivity and specificity for mucinous lesions are approximately 62% and 93%, respectively, at this concentration. Cyst fluid CEA concentrations of 5 ng/mL and below indicate a low risk for a mucinous cyst, and are more consistent with serous cystadenoma, fluid collections complicating pancreatitis, cystic neuroendocrine tumor, or metastatic lesions. CEA values between these extremes have limited diagnostic value.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

Carcinoembryonic Antigen (CEA), Peritoneal Fluid

**Clinical Information:** Malignancy accounts for approximately 7% of cases of ascites formation. Malignant disease can cause ascites by various mechanisms including: peritoneal carcinomatosis (53%), massive liver metastasis causing portal hypertension (13%), peritoneal carcinomatosis plus massive liver metastasis (13%), hepatocellular carcinoma plus cirrhosis (7%), and chylous ascites due to lymphoma (7%). The evaluation and diagnosis of malignancy-related ascites is based on the patient clinical history, ascites fluid analysis, and imaging tests. The overall sensitivity of cytology for the detection of malignancy-related ascites ranges from 58% to 75%. Cytology examination is most successful in patients with ascites related to peritoneal carcinomatosis as viable malignant cells are exfoliated into the ascitic fluid. However, only approximately 53% of patients with malignancy-related ascites have peritoneal carcinomatosis. Patients with other causes of malignancy-related ascites almost always have a negative cytology. Carcinoembryonic antigen (CEA) is a glycoprotein that is shed from the surface of malignant cells. Measurement of CEA in ascitic fluid has been proposed as a helpful test in detecting malignancy-related ascites given the limited sensitivity of cytology.

**Useful For:** An adjunct to cytology to differentiate between malignancy-related and benign causes of ascites formation

**Interpretation:** A peritoneal fluid carcinoembryonic antigen (CEA) concentration >6.0 ng/mL is suspicious but not diagnostic of malignancy-related ascites. This clinical decision limit cutoff yielded 48% sensitivity and 99% specificity in a study of 137 patients presenting with ascites. CEA
concentrations were significantly higher in ascites caused by malignancies known to be associated with elevated serum CEA levels including lung, breast, ovarian, gastrointestinal, and colorectal cancers. However, ascites caused by other malignancies such as lymphoma, mesothelioma, leukemia, and melanoma and hepatocellular carcinoma, routinely had CEA concentrations <6.0 ng/mL. Therefore, negative results should be interpreted with caution, especially in patients who have or are suspected of having a malignancy not associated with elevated CEA levels in serum.

Reference Values:
An interpretive report will be provided.


Carcinoembryonic Antigen (CEA), Pleural Fluid

Clinical Information: Pleural effusions occur as a consequence of either nonmalignant conditions (including congestive heart failure, pneumonia, pulmonary embolism, and liver cirrhosis) or malignant conditions (including lung, breast, and lymphoma cancers). Diagnosing the cause of an effusion can be difficult, often requiring cytological examination of the pleural fluid and imaging studies of the pleural tissue. Analysis of various tumor markers in pleural fluid has shown that these markers can differentiate between effusions caused by nonmalignant and malignant conditions and can enhance cytology and imaging findings. Carcinoembryonic antigen (CEA) is a glycoprotein produced during fetal development. Nonsmoking, healthy adults typically produce low to undetectable levels of CEA. Serum concentrations of CEA may be elevated in patients with certain malignancies that secrete CEA into circulation, including medullary thyroid carcinoma and breast, gastrointestinal tract, colorectal, liver, lung, ovarian, pancreatic, and prostate cancers. Pleural fluid concentrations of CEA have been reported to be elevated in patients with certain malignancies. Malignancies that can secrete CEA and elevate serum CEA concentrations, including lung, breast, ovarian, gastrointestinal, and colorectal cancers, typically also elevate CEA in pleural fluid. In contrast, malignancies that do not secrete CEA, including mesothelioma, lymphoma, leukemia, and melanoma, have low concentrations of CEA in pleural fluid comparable to concentrations observed in non-malignant effusions. Elevated CEA concentrations in pleural fluid have also been reported with certain nonmalignant conditions, including liver cirrhosis, pancreatitis, complicated parapneumonic effusions and empyemas, and rarely with tuberculosis. CEA results should be used in conjunction with cytological analysis of pleural fluid, imaging studies, and other clinical findings.

Useful For: An adjuvant to cytology and imaging studies to differentiate between nonmalignant and malignant causes of pleural effusions

Interpretation: A pleural fluid carcinoembryonic antigen (CEA) concentration of 3.5 ng/mL or higher is suspicious but not diagnostic of a malignant source of the effusion. This cutoff yielded a sensitivity of 52%, specificity of 95%, and part per volume of 93% in a study of 200 patients presenting with effusion. CEA concentrations were significantly higher in effusions caused by CEA-secreting malignancies, including lung, breast, ovarian, gastrointestinal, and colorectal cancers. However, effusions caused by non-CEA-secreting malignancies, including lymphoma, mesothelioma, leukemia, and melanoma, routinely had CEA concentrations below 3.5 ng/mL. Therefore, negative results should be interpreted with caution, especially in patients who have or are suspected of having a non-CEA-secreting malignancy. Correlation of all tumor marker results with cytology and imaging is highly recommended.

Reference Values:
An interpretive report will be provided.

Carcinoembryonic Antigen (CEA), Serum

**Clinical Information**: Carcinoembryonic antigen (CEA) is a glycoprotein normally found in embryonic entodermal epithelium. Increased levels may be found in patients with primary colorectal cancer or other malignancies including medullary thyroid carcinoma and breast, gastrointestinal tract, liver, lung, ovarian, pancreatic, and prostatic cancers. Serial monitoring of CEA should begin prior to therapy to verify post therapy decrease in concentration and to establish a baseline for evaluating possible recurrence. Levels generally return to normal within 1 to 4 months after removal of cancerous tissue.

**Useful For**: Monitoring colorectal cancer and selected other cancers such as medullary thyroid carcinoma. May be useful in assessing the effectiveness of chemotherapy or radiation treatment. Carcinoembryonic antigen levels are not useful in screening the general population for undetected cancers.

**Interpretation**: Grossly elevated carcinoembryonic antigen (CEA) concentrations (>20 ng/mL) in a patient with compatible symptoms are strongly suggestive of the presence of cancer and also suggest metastasis. Most healthy subjects (97%) have values ≤3.0 ng/mL. After removal of a colorectal tumor, the serum CEA concentration should return to normal by 6 weeks, unless there is residual tumor. Increases in test values over time in a patient with a history of cancer suggest tumor recurrence.

**Reference Values**: Nonsmokers: ≤3.0 ng/mL
Some smokers may have elevated CEA, usually ≤5.0 ng/mL.


Carcinoembryonic Antigen (CEA), Spinal Fluid

**Clinical Information**: Carcinoembryonic antigen (CEA) normally is present in cerebrospinal fluid (CSF) in very low concentrations. Elevations in serum CEA can cause passive transfer to CSF. Tumors of the brain, especially metastatic tumors, can elevate CSF CEA.

**Useful For**: Detecting meningeal carcinomatosis and intradural or extradural infiltration. Differentiating brain parenchymal metastasis from adenocarcinoma or squamous-cell carcinoma.

**Interpretation**: Increased values are seen in approximately 60% of patients with meningeal carcinomatosis.

**Reference Values**: <0.6 ng/mL

Carcinoembryonic Antigen, monoclonal (mCEA) Immunostain, Technical Component Only

**Clinical Information:** In tissue sections of normal colon, carcinoembryonic antigen (CEA) is mainly localized at the apical border of the epithelial cells. Monoclonal CEA antibodies label the epithelium of colonic adenocarcinoma, normal adult colonic mucosa, and normal gastric foveolar mucus-producing cells.

**Useful For:** Marker of epithelial cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

Carcinoembryonic Antigen, polyclonal (pCEA) Immunostain, Technical Component Only

**Clinical Information:** Carcinoembryonic antigen, polyclonal (P-CEA) labels normal and neoplastic epithelium of the small and large intestine, stomach, and pancreatic ducts. The polyclonal antibody also reacts with biliary canaliculi and granulocytes.

**Useful For:** Marker of epithelial cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a

Cardamom, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**Cardiac Fibrinogen, Plasma**

**Clinical Information:** Elevated plasma fibrinogen is a risk factor for cardiovascular disease. Fibrinogen contributes to cardiovascular disease risk through a variety of mechanisms. Plasma viscosity is strongly influenced by fibrinogen concentrations. Fibrinogen is an acute-phase reactant indicative of chronic inflammatory status. Most importantly, fibrinogen and its enzymatic degradation product fibrin bind specifically to activated platelets to promote platelet aggregation and blood clotting. Carotid intimamedia thickness, a radiological measure of atherosclerosis, is significantly correlated with plasma fibrinogen concentrations. Addition of plasma fibrinogen measurement to a prognostic model for cardiovascular disease that includes age, gender, tobacco use, blood pressure, history of diabetes, high density lipoprotein, and total cholesterol significantly improves 10-year risk classification. Fibrinogen assessment in patients at intermediate risk according to conventional biomarkers significantly improves classification. Plasma fibrinogen concentrations can be significantly lowered by smoking cessation and increased physical activity.

**Useful For:** Evaluating risk of atherosclerosis and adverse events related to atherosclerotic disease

**Interpretation:** Elevated plasma fibrinogen confers increased risk of atherosclerosis, acute myocardial infarction, and stroke.

**Reference Values:**
- <340 mg/dL 1st quartile (low risk)
- 340-390 mg/dL 2nd quartile
- 391-450 mg/dL 3rd quartile
- >450 mg/dL 4th quartile (high risk)

**Clinical References:**

**Cardiovascular Risk Marker Panel, Serum**

**Clinical Information:** Cardiovascular disease is the number 1 cause of death in the United States with an estimated 1.5 million heart attacks and 0.5 million strokes occurring annually. Many of these events occur in individuals who have no prior symptoms. Standard risk factors, including age, smoking status, hypertension, diabetes, cholesterol, and HDL cholesterol, predict only about 65% of individuals who will go on to have a cardiovascular event. Therefore, identification of patients with residual risk is important to target lifestyle and pharmaceutical intervention to those at higher risk of future events. Many additional risk markers have been identified for cardiovascular disease but few have emerged as independent risk markers. Two of these additional risk markers, high-sensitivity C-reactive protein (hsCRP) and lipoprotein (a) (Lp[a]), are clearly shown to be independently associated with increased risk of future cardiovascular events. Several recent guidelines have suggested that clinicians utilize hsCRP and Lp[a] in selected persons to augment risk classification, guide intensity of risk-reduction therapy and modulate clinical judgment when making therapeutic decision. Prospective studies assessing these risk factors individually have determined them to be independently associated with increased risk for the development of ischemic events. Guidelines recommend measurement of additional risk markers in individuals who are at intermediate risk for developing cardiovascular disease, those with early atherosclerosis without explanation by abnormalities of traditional risk factors, and those with a strong family history of cardiovascular disease without the presence of traditional risk factors.

**Useful For:** Assessment for risk of developing cardiovascular disease, major adverse cardiovascular
events, or ischemic cerebrovascular events

**Interpretation:** Specific interpretations are provided based on lipid results according to Mayo Clinic care process models. Mayo Clinic has adopted the National Lipid Association classifications, which are included as reference values on Mayo Clinic and Mayo Medical Laboratories reports (see Reference Values). More aggressive treatment strategies may be pursued in patients determined to be at increased risk.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age</th>
<th>2-17 years</th>
<th>&gt;18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-HDL Cholesterol (mg/dL)</td>
<td>** Acceptable: high: 120-144 High: &gt; or =145</td>
<td>* Desirable: Above Desirable: 130-159 mg/dL. Borderline high: 160-189 mg/dL. High: 190-219 mg/dL. Very high: &gt; or =220 mg/dL</td>
</tr>
<tr>
<td>LDL Cholesterol (mg/dL)</td>
<td>** Acceptable: high: 110-129 High: &gt; or =130</td>
<td>*** Desirable: Desirable: 100-129 Borderline high: 130-159 High: 160-189 Very high: &gt; or =190</td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dL)</td>
<td>** Low: low: 40-45 Acceptable: &gt; 45 *** Males: &gt; or =40 Females: &gt; or =50</td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>** Acceptable: high: 170-199 High: &gt; or =200</td>
<td>* Desirable: &lt; 200 Borderline high: 200 - 239 High: &gt; or = 240</td>
</tr>
<tr>
<td>LIPOPROTEIN (a) (mg/dL)</td>
<td>&lt; or =30 mg/dL. Values &gt;30 mg/dL may suggest increased risk of coronary heart disease.</td>
<td>&lt; or =30 mg/dL. Values &gt;30 mg/dL may suggest increased risk of coronary heart disease.</td>
</tr>
<tr>
<td>C-REACTIVE PROTEIN HIGH SENSITIVITY</td>
<td>* Lower risk: Higher risk: &gt;=2.0 mg/L * Lower risk: Higher risk: &gt;=2.0 mg/L</td>
<td>Acute inflammation: &gt;10.0 mg/L Acute inflammation: &gt;10.0 mg/L</td>
</tr>
</tbody>
</table>

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal 1 0.35-0.69 Low Positive 2 0.70-3.4 Moderate Positive 3 3.5-17.4 High Positive 4 17.5-49.9 Very High Positive 5 50.0-99.9 Very High Positive 6 > or = 100 Very High Positive

Reference Values: <0.35 kU/L

CPT2Z 35398

Carnitine Palmitoyltransferase II Deficiency, Full Gene Analysis

Clinical Information: Carnitine palmitoyltransferase II (CPT II) deficiency is an autosomal recessive disorder of long-chain fatty-acid oxidation. There are 3 distinct clinical phenotypes: a lethal neonatal form, an early-onset infantile form, and a late-onset adult myopathic form. The lethal neonatal and early-onset infantile forms are characterized by liver failure, cardiomyopathy, seizures, hypoketotic hypoglycemia, peripheral myopathy and early death. The adult-onset myopathic form is the most common type and is characterized by exercise-induced muscle pain and weakness and may be associated with myoglobinuria. Males are more likely to be affected with the myopathic form than females. Initial screening can be done with plasma acylcarnitines. Definitive diagnosis can be made by detection of reduced CPT enzyme activity. Mutations in the CPT2 gene are responsible for CPT II deficiency and sequencing of this gene is recommended after positive biochemical analysis.

Useful For: Confirmation of diagnosis of carnitine palmitoyltransferase II deficiency Carrier screening in cases where there is a family history of carnitine palmitoyltransferase II deficiency, but disease-causing mutations have not been identified in an affected individual

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


CARN 8802

Carnitine, Plasma

Clinical Information: Carnitine and its esters are required for normal energy metabolism and serve 4 primary functions: -Importing long-chain fatty acids into the mitochondria -Exporting naturally-occurring short-chain acyl-CoA groups from the mitochondria -Buffering the ratio of free CoA to esterified CoA -Removing potentially toxic acyl-CoA groups from the cells and tissues Evaluation of carnitine in serum, plasma, tissue, and urine screens patients for suspected primary disorders of the carnitine cycle, or secondary disturbances in carnitine levels as a result of organic acidemias and fatty acid oxidation disorders. In the latter disorders, acyl-CoA groups accumulate and are excreted into the urine and bile as carnitine derivatives, resulting in a secondary carnitine deficiency. More than 100 such primary and secondary disorders have been described. Individually, the incidence of these disorders varies from less than 1 in 10,000 to more than 1 in 1,000,000 live births. Collectively, their incidence is approximately 1 in 1,000 live births. Primary carnitine deficiency has an incidence of approximately 1 in 21,000 live births based on Minnesota newborn screening data. Other conditions which could cause an abnormal carnitine level are neuromuscular diseases, gastrointestinal disorders, familial cardiomyopathy, renal tubulopathies and chronic renal failure (dialysis), and prolonged treatment with steroids, antibiotics (pivalic acid), anticonvulsants (valproic acid), and total parenteral
nutrition. Follow-up testing is required to differentiate primary and secondary carnitine deficiencies and to elucidate the exact cause.

**Useful For:** Evaluation of patients with a clinical suspicion of a wide range of conditions including organic acidemias, fatty acid oxidation disorders, and primary carnitine deficiency in plasma specimens

**Interpretation:** When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Total Carnitine (TC) Range*</th>
<th>Free Carnitine (FC) Range*</th>
<th>Acylcarnitine (AC) Range*</th>
<th>AC/FC Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; or =1 day</td>
<td>23-68</td>
<td>12-36</td>
<td>7-37</td>
<td>0.4-1.7</td>
</tr>
<tr>
<td>2-7 days</td>
<td>17-41</td>
<td>10-21</td>
<td>3-24</td>
<td>0.2-1.4</td>
</tr>
<tr>
<td>8-31 days</td>
<td>19-59</td>
<td>12-46</td>
<td>4-15</td>
<td>0.1-0.7</td>
</tr>
<tr>
<td>32 days-12 months</td>
<td>38-68</td>
<td>27-49</td>
<td>7-19</td>
<td>0.2-0.5</td>
</tr>
<tr>
<td>13 months-6 years</td>
<td>35-84</td>
<td>24-63</td>
<td>4-28</td>
<td>0.1-0.9</td>
</tr>
<tr>
<td>7-10 years</td>
<td>28-83</td>
<td>22-66</td>
<td>3-32</td>
<td>0.1-0.9</td>
</tr>
<tr>
<td>11-17 years</td>
<td>34-77</td>
<td>22-65</td>
<td>4-29</td>
<td>0.1-0.9</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td>34-78</td>
<td>25-54</td>
<td>5-30</td>
<td>0.1-0.8</td>
</tr>
</tbody>
</table>

*Values expressed as nmol/mL.


**Clinical References:**


**Carnitine, Serum**

**Clinical Information:** Carnitine and its esters are required for normal energy metabolism and serve 4 primary functions: -Importing long-chain fatty acids into the mitochondria -Exporting naturally-occurring short-chain acyl-CoA groups from the mitochondria -Buffering the ratio of free CoA to esterified CoA -Removing potentially toxic acyl-CoA groups from the cells and tissues Evaluation of carnitine in serum, plasma, tissue, and urine screens patients for suspected primary disorders of the carnitine cycle, or secondary disturbances in carnitine levels as a result of organic acidemias and fatty acid oxidation disorders. In the latter disorders, acyl-CoA groups accumulate and are excreted into the urine and bile as carnitine derivatives, resulting in a secondary carnitine deficiency. More than 100 such primary and secondary disorders have been described. Individually, the incidence of these disorders varies from less than 1 in 10,000 to more than 1 in 1,000,000 live births. Collectively, their incidence is approximately 1 in 1,000 live births. Primary carnitine deficiency has an incidence of approximately 1 in 21,000 live births based on Minnesota newborn screening data. Other conditions which could cause an abnormal carnitine
level are neuromuscular diseases, gastrointestinal disorders, familial cardiomyopathy, renal tubulopathies and chronic renal failure (dialysis), and prolonged treatment with steroids, antibiotics (pivalic acid), anticonvulsants (valproic acid), and total parenteral nutrition. Follow-up testing is required to differentiate primary and secondary carnitine deficiencies and to elucidate the exact cause.

**Useful For:** Evaluation of patients with a clinical suspicion of a wide range of conditions including organic acidemias, fatty acid oxidation disorders, and primary carnitine deficiency in serum specimens

**Interpretation:** When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

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<th>Acylcarnitine (AC)</th>
<th>AC/FC Ratio</th>
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<td>&lt; or =1 day</td>
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<td>Range</td>
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<td>12-36</td>
<td>7-37</td>
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<td>3-24</td>
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<td>27-49</td>
<td>7-19</td>
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</tr>
<tr>
<td>&gt; or =18 years</td>
<td>22-65</td>
<td>4-29</td>
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<td></td>
</tr>
</tbody>
</table>

*Values expressed as nmol/mL


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**Clinical References:**

**CARNU 81123**

Carnitine, Urine

**Clinical Information:** Carnitine and its esters are required for normal energy metabolism and serve 4 primary functions: -Importing long-chain fatty acids into the mitochondria -Exporting naturally occurring short-chain acyl-CoA groups from the mitochondria -Buffering the ratio of free CoA to esterified CoA -Removing potentially toxic acyl-CoA groups from the cells and tissues Evaluation of carnitine in serum, plasma, tissue, and urine screens patients for suspected primary disorders of the carnitine cycle, or secondary disturbances in carnitine levels as a result of organic acidemias and fatty acid oxidation disorders. In the latter, acyl-CoA groups accumulate and are excreted into the urine and bile as carnitine derivatives, resulting in a secondary carnitine deficiency. More than 100 such primary and secondary disorders have been described. Individually, the incidence of these disorders varies from...
<1 in 10,000 to >1 in 1,000,000 live births. Collectively, their incidence is approximately 1 in 1,000 live births. Primary carnitine deficiency has an incidence of approximately 1 in 21,000 live births based on Minnesota newborn screening data. Other conditions which could cause an abnormal carnitine level include neuromuscular diseases, gastrointestinal disorders, familial cardiomyopathy, renal tubulopathies and chronic renal failure (dialysis), and prolonged treatment with steroids, antibiotics (pivalic acid), anticonvulsants (valproic acid), and total parenteral nutrition. Follow-up testing is required to differentiate primary and secondary carnitine deficiencies and to elucidate the exact cause.

**Useful For:** Evaluation of patients with a clinical suspicion of a wide range of conditions including organic acidemias and fatty acid oxidation disorders Monitoring carnitine treatment

**Interpretation:** When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

**FREE**

77-214 nmol/mg of creatinine

**TOTAL**

180-412 nmol/mg of creatinine

**RATIO**

Acyl to free: 0.7-3.4

**Clinical References:**


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**CACTZ 35379**

**Carnitine-Acylcarnitine Translocase Deficiency, Full Gene Analysis**

**Clinical Information:** Carnitine-acylcarnitine translocase (CACT) deficiency is a rare autosomal recessive disorder of fatty acid oxidation. The disease typically presents in the neonatal period with severe hypoketotic hypoglycemia, hyperammonemia, cardiac abnormalities, hepatic dysfunction, skeletal muscle weakness, encephalopathy, and early death. However, presentations at a later age with a milder phenotype have also been reported. Initial screening can be done with plasma acylcarnitines. Definitive diagnosis can be made by detection of reduced CACT enzyme activity. Mutations in the SLC25A20 gene are responsible for CACT deficiency, and sequencing of this gene is recommended after positive biochemical analysis.

**Useful For:** Confirmation of diagnosis of carnitine-acylcarnitine translocase (CACT) deficiency Carrier screening in cases where there is a family history of CACT deficiency, but disease-causing mutations have not been identified in an affected individual

**Reference Values:**

An interpretive report will be provided.

**Clinical References:**

CAROB

**Carob, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


FCARO

**Carotene, Beta**

**Useful For:** Confirm the diagnosis of carotenoderma; detect fat malabsorption; depressed carotene levels may be found in cases of steatorrhea.

**Interpretation:** High levels are useful to rule out steatorrhea but lower values lack specificity. There is poor sensitivity. High in the serum of those ingesting large amounts of vegetables.

**Reference Values:**

3 - 91 ug/dL
**Carrot IgG**

**Interpretation:** mcg/mL of IgG  
Lower Limit of Quantitation 2.0  
Upper Limit of Quantitation 200

**Reference Values:**  
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Carrot, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Clinical References:** Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and
**Casein IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation* 2.0 Upper Limit of Quantitation** 200

**Reference Values:**
< 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Casein, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<th>Class IgE kU/L</th>
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</tbody>
</table>

Reference values apply to all ages.

**FCASH**

**Cashew IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

< 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**CASH**

**Cashew, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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CASRZ 37439

CASR Gene, Full Gene Analysis

Clinical Information: The extracellular G-protein-coupled calcium-sensing receptor (CASR) is an essential component of calcium homeostasis. CASR is expressed at particularly high levels in the parathyroid glands and kidneys. It forms stable homodimeric cell-membrane complexes, which signal upon binding of extracellular calcium ions (Ca++) in the parathyroid glands, this results in downregulation of gene expression of the main short-term regulator of calcium homeostasis, parathyroid hormone (PTH), as well as diminished secretion of already synthesized PTH. At the same time, renal calcium excretion is upregulated and sodium chloride excretion is downregulated. Ca(++) binding to CASR is highly cooperative within the physiological Ca(++) concentration range, leading to a steep dose-response curve, which results in tight control of serum calcium levels. To date, over 100 different alterations in the CASR gene have been described. Many of these cause diseases of abnormal serum calcium regulation. Inactivating mutations result in undersensing of Ca(++) concentrations and consequent PTH overproduction and secretion. This leads to either familial hypocalciuric hypercalcemia (FHH) or neonatal severe primary hyperparathyroidism (NSPHT), depending on the severity of the functional impairment. Except for a very small percentage of cases with no apparent CASR mutations, FHH is due to heterozygous inactivating CASR mutations. Serum calcium levels are mildly-to-moderately elevated. PTH is within the reference range or modestly elevated, phosphate is normal or slightly low, and urinary calcium excretion is low for the degree of hypercalcemia. Unlike patients with primary hyperparathyroidism (PHT), which can be difficult to distinguish from FHH, the majority of FHH patients do not seem to suffer any adverse long-term effects from hypercalcemia and elevated PTH levels. They should, therefore, generally not undergo parathyroidectomy. NSPHT is usually due to homozygous or compound heterozygous inactivating CASR mutations, but can occasionally be caused by dominant-negative heterozygous mutations. The condition presents at birth, or shortly thereafter, with severe hypercalcemia requiring urgent parathyroidectomy. Activating mutations lead to oversensing of Ca(++), resulting in suppression of PTH secretion and consequently hypoparathyroidism. All activating mutations described are functionally dominant and disease inheritance is therefore autosomal dominant. However, sporadic cases also occur. Autosomal dominant hypoparathyroidism caused by CASR mutations may account for many cases of idiopathic hypoparathyroidism. Disease severity depends on the degree of gain of function, spanning the spectrum from mild hypoparathyroidism, which is diagnosed incidentally, to severe and early onset disease. In addition, while the majority of patients suffer only from hypoparathyroidism, a small subgroup with extreme gain of function mutations suffer from concomitant inhibition of renal sodium chloride transport. These individuals may present with additional symptoms of hypokalemic metabolic alkalosis, hyperreninemia, hyperaldosteronism, and hypomagnesemia, consistent with type V Bartter syndrome.

Useful For: Establishing a diagnosis of familial hypocalciuric hypercalcemia As part of the workup of some patients with primary hyperparathyroidism Establishing a diagnosis of neonatal severe primary hyperparathyroidism Establishing a diagnosis of autosomal dominant hypoparathyroidism As part of the workup of idiopathic hypoparathyroidism As part of the workup of patients with Bartter syndrome

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.
Reference Values:
An interpretive report will be provided


Castor Bean, IgE
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.

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**Cat Epithelium, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>4</td>
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Reference values apply to all ages.


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**COMTV**

**Catechol-O-Methyltransferase (COMT) Genotype**

**Clinical Information:** Catechol-O-methyltransferase (COMT) is involved in phase II (conjugative) metabolism of catecholamines and catechol drugs, such as dopamine, as well as the catechol-estrogens. COMT transfers a donor methyl-group from S-adenosylmethionine to acceptor hydroxy groups on catechol structures (aromatic ring structures with vicinal hydroxy-groups).(1) Bioactive catecholamine

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metabolites are metabolized by COMT in conjunction with monoamine oxidase (MAO):
- Norepinephrine is methylated by COMT forming normetanephrine. -Epinephrine is methylated by COMT forming metanephrine. -Dopamine is converted to homovanillic acid through the combined action of MAO and COMT. Parkinsonism patients receiving levodopa (L-DOPA) therapy are frequently also prescribed a COMT inhibitor to minimize metabolism of L-DOPA by COMT, thereby prolonging L-DOPA action. COMT is also involved in the inactivation of estrogens. Estradiol can be hydroxylated forming the catechol estrogens 2-hydroxyestradiol and 4-hydroxyestradiol.(2) These hydroxylated estriadiols are methylated by COMT, forming the corresponding methoxyestradiols. The gene encoding COMT is transcribed from alternative promoters to produce 2 forms of the enzyme, a soluble short form and a membrane-bound long form. Variants in the COMT gene are therefore designated in the literature by the position of the amino acid change in both the short and long form of the enzyme. A single nucleotide polymorphism (SNP) in exon 4 of the gene produces an amino acid change from valine to methionine (Val108/158Met). The presence of methionine at this position reduces the maximum activity of the variant enzyme by 25% and also results in significantly less immunoreactive COMT protein, resulting in a 3-fold to 4-fold decrease in activity compared to wild type (valine at this position). This variant has been associated with prediction of response and risk of relapse when using nicotine replacement therapy for smoking cessation.(3) The following information outlines the relationship between the polymorphism detected in this assay and the effect on the activity of the enzyme produced by that allele: Amino Acid Change cDNA Nucleotide Change Effect on Enzyme Activity/Metabolism None (wild-type) None (wild type) Normal activity Val108/158Met 472G->A Reduced activity

**Useful For:** Prediction of response to nicotine replacement therapy for smoking cessation Investigation of inhibitor dosing for decreasing levodopa metabolism Research use for assessing estrogen metabolism

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Catecholamine Fractionation, Free, 24 Hour, Urine**

**Clinical Information:** The catecholamines (dopamine, epinephrine, and norepinephrine) are derived from tyrosine via a series of enzymatic conversions. All 3 catecholamines are important neurotransmitters in the central nervous system and play crucial roles in the autonomic regulation of many homeostatic functions, namely, vascular tone, intestinal and bronchial smooth muscle tone, cardiac rate and contractility, and glucose metabolism. Their actions are mediated via alpha and beta adrenergic receptors and dopamine receptors, all existing in several subforms. The 3 catecholamines overlap but also differ in their receptor activation profile and consequent biological actions. The systematically circulating fraction of the catecholamines is derived almost exclusively from the adrenal medulla, with small contributions from sympathetic ganglia. They are normally present in the plasma in minute amounts, but levels can increase dramatically and rapidly in response to change in posture, environmental temperature, physical and emotional stress, hypovolemia, blood loss, hypotension, hypoglycemia, and exercise. In patients with pheochromocytoma, a potentially curable tumor of catecholamine producing cells of the adrenal medulla, or less commonly of sympathetic ganglia (paraganglioma), urine catecholamine levels may be elevated.
This results in episodic or sustained hypertension and often in intermittent attacks of palpitations, cardiac arrhythmias, headache, sweating, pallor, anxiety, tremor, and nausea ("spells"). Elevations of the urine levels of 1 or several of the catecholamines also may be observed in patients with neuroblastoma and related tumors (ganglioneuroblastomas and ganglioneuromas) and, very occasionally, in other neuroectodermal tumors. At the other end of the spectrum, inherited and acquired syndromes of autonomic dysfunction/failure and autonomic neuropathies are characterized by either inadequate production of 1 or several of the catecholamines, or by insufficient release of catecholamines upon appropriate physiological stimuli (eg, change in posture from supine to standing, cold exposure, exercise, stress).

**Useful For:** An auxiliary test to fractionated plasma and urine metanephrine measurements in the diagnosis of pheochromocytoma and paraganglioma An auxiliary test to urine vanillylmandelic acid and homovanillic acid determination in the diagnosis and follow-up of patients with neuroblastoma and related tumors

**Interpretation:** Diagnosis of Pheochromocytoma: This test should not be used as the first-line test for pheochromocytoma. PMET / Metanephrines, Fractionated, Free, Plasma (the most sensitive assay) and/or METAF / Metanephrines, Fractionated, 24 Hour, Urine (almost as sensitive and highly specific) are the recommended first-line laboratory tests for pheochromocytoma. However, urine catecholamine measurements can still be useful in patients whose plasma metanephrines or urine metanephrines measurements do not completely exclude the diagnosis. In such cases, urine catecholamine specimens have an 86% diagnostic sensitivity when cut-offs of >80 mg/24 hour for norepinephrine and >20 mg/24 hour for epinephrine are employed. Unfortunately, the specificity of these cut-off levels for separating tumor patients from other patients with similar symptoms is only 88%. When more specific (98%) decision levels of >170 mg/24 hours for norepinephrine or >35 mg/24 hours for epinephrine are used, the assay's sensitivity falls to about 77%. Diagnosis of Neuroblastoma: Vanillylmandelic acid, homovanillic acid, and sometimes urine catecholamine measurements on spot urine or 24-hour urine are the mainstay of biochemical diagnosis and follow-up of neuroblastoma; 1 or more of these tests may be elevated.

**Reference Values:**

**NOREPINEPHRINE**

- <1 year: <11 mcg/24 hours
- 1 year: 1-17 mcg/24 hours
- 2-3 years: 4-29 mcg/24 hours
- 4-6 years: 8-45 mcg/24 hours
- 7-9 years: 13-65 mcg/24 hours
- > or =10 years: 15-80 mcg/24 hours

**EPINEPHRINE**

- <1 year: <2.6 mcg/24 hours
- 1 year: <3.6 mcg/24 hours
- 2-3 years: <6.1 mcg/24 hours
- 4-9 years: 0.2-10.0 mcg/24 hours
- 10-15 years: 0.5-20.0 mcg/24 hours
- > or =16 years: <21 mcg/24 hours

**DOPAMINE**

- <1 year: <86 mcg/24 hours
- 1 year: 10-140 mcg/24 hours
- 2-3 years: 40-260 mcg/24 hours
- > or =4 years: 65-400 mcg/24 hours

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.

**Catecholamine Fractionation, Free, Plasma**

**Clinical Information:** The catecholamines (dopamine, epinephrine, and norepinephrine) are derived from tyrosine via a series of enzymatic conversions. All 3 catecholamines are important neurotransmitters in the central nervous system and also play a crucial role in the autonomic regulation of many homeostatic functions, namely, vascular tone, intestinal and bronchial smooth muscle tone, cardiac rate and contractility, and glucose metabolism. Their actions are mediated via alpha and beta adrenergic receptors and dopamine receptors, all existing in several subforms. The 3 catecholamines overlap, but also differ in their receptor activation profile and consequent biological actions. The systemically circulating fraction of the catecholamines is derived almost exclusively from the adrenal medulla, with small contributions from sympathetic ganglia. The catecholamines are normally present in the plasma in minute amounts, but levels can increase dramatically and rapidly in response to change in posture, environmental temperature, physical and emotional stress, hypovolemia, blood loss, hypotension, hypoglycemia, and exercise. In patients with pheochromocytoma (a potentially curable tumor of catecholamine-producing cells of the adrenal medulla), or less commonly of sympathetic ganglia (paraganglioma), plasma catecholamine levels may be continuously or episodically elevated. This results in episodic or sustained hypertension and in intermittent attacks of palpitations, cardiac arrhythmias, headache, sweating, pallor, anxiety, tremor, and nausea. Intermittent or continuous elevations of the plasma levels of 1 or several of the catecholamines may also be observed in patients with neuroblastoma and related tumors (ganglioneuroblastomas and ganglioneurolemomas) and, very occasionally, in other neuroectodermal tumors. At the other end of the spectrum, inherited and acquired syndromes of autonomic dysfunction or failure and autonomic neuropathies are characterized by either inadequate production of 1 or several of the catecholamines or by insufficient release of catecholamines upon appropriate physiological stimuli (eg, change in posture from supine to standing, cold exposure, exercise, stress).

**Useful For:** Diagnosis of pheochromocytoma and paraganglioma, as an auxiliary test to fractionated plasma and urine metanephrine measurements (plasma metanephrine is the preferred test for this diagnosis) Diagnosis and follow-up of patients with neuroblastoma and related tumors, as an auxiliary test to urine vanillylmandelic acid and homovanillic acid measurements Evaluation of patients with autonomic dysfunction or failure or autonomic neuropathy

**Interpretation:** Diagnosis of Pheochromocytoma: This test should not be used as the first-line test for pheochromocytoma, as plasma catecholamine levels may not be continuously elevated, but only secreted during a “spell.” By contrast, production of metanephrines (catecholamine metabolites) appears to be increased continuously. The recommended first-line laboratory tests for pheochromocytoma are: -PMET / Metanephrines, Fractionated, Free, Plasma: the most sensitive assay -METAF / Metanephrines, Fractionated, 24 Hour, Urine: highly specific and almost as sensitive as PMET However, plasma catecholamine measurements can still be useful in patients whose plasma metanephrine or urine metanephrine measurements do not completely exclude the diagnosis. In such cases, plasma catecholamine specimens, if drawn during a “spell,” have a 90% to 95% diagnostic sensitivity when cutoffs of >750 pg/mL for norepinephrine and >110 pg/mL for epinephrine are employed. A lower value during a “spell,” particularly when plasma or urinary metanephrine measurements were also normal, essentially rules out pheochromocytoma. Unfortunately, the specificity of these high-sensitivity cutoff levels is not good for separating tumor patients from other patients with similar symptoms. When more specific (95%) decision levels of 2,000 pg/mL for norepinephrine or 200 pg/mL for epinephrine are used, the assay’s sensitivity falls to about 85%. Diagnosis of Neuroblastoma: Vanillylmandelic acid, homovanillic acid, and sometimes urine catecholamine measurements on spot urine or 24-hour urine are the mainstay of biochemical diagnosis and follow-up of neuroblastoma. Plasma catecholamine levels can aid diagnosis in some cases, but diagnostic decision levels are not well established. The most useful finding is disproportional elevations in 1 of the 3 catecholamines, particularly dopamine, which may be
observed in these tumors. Diagnosis of Autonomic Dysfunction or Failure and Autonomic Neuropathy: Depending on the underlying cause and pathology, autonomic dysfunction or failure and autonomic neuropathies are associated with subnormal resting norepinephrine levels, or an absent rise of catecholamine levels in response to physiological release stimuli (eg, change in posture from supine to standing, cold exposure, exercise, stress), or both. In addition, there may be significant abnormalities in the ratios of the plasma values of the catecholamines to each other (normal: norepinephrine>epinephrine>dopamine). This is observed most strikingly in the inherited dysautonomic disorder dopamine-beta-hydroxylase deficiency, which results in markedly elevated plasma dopamine levels and a virtually total absence of plasma epinephrine and norepinephrine.

**Reference Values:**

**NOREPINEPHRINE**
- Supine: 70-750 pg/mL
- Standing: 200-1,700 pg/mL

**EPINEPHRINE**
- Supine: < or =111 pg/mL
- Standing: < or =141 pg/mL

**DOPAMINE**
- <30 pg/mL (no postural change)

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.

**Clinical References:**

**FCATE 57554**

**Catfish (Siluriformes spp) IgE**

**Interpretation:**
Class IgE (kU/L) Comment
0 <0.10 Negative 0/1
0.10-0.34 Equivocal 1
0.35-0.69 Low Positive 2
0.70-3.4 Moderate Positive 3
3.5-17.4 High Positive 4
17.5-49.9 Very High Positive 5
50.0-99.9 Very High Positive 6
100 Very High Positive 7

**Reference Values:**
<0.35 kU/L

**FCLPS 91193**

**Cathartic Laxatives Profile, Stool**

**Reference Values:**
Reporting limit determined each analysis

**Magnesium (mg/g)**

Magnesium concentrations in stool water above the normal levels of 0.7-1.2 mg/mL have been indicative of surreptitious abuse of magnesium containing laxatives.

NMS Labs Calculated Normal: approximately 0.5-10 mg/g (Based on the reported range of magnesium eliminated per day in stool and the range of stool mass per day in adults).
Not for clinical diagnostic purposes.

**Phosphorus (mg/g)**

Phosphorus concentration in stool water averaged 1.8 +/- 0.3 mg/mL (ranged from 0.3-4.2 mg/mL) following administration of 105 mmol of sodium phosphate.

NMS Labs calculated normal: approximately 1.4-22 mg/g (Based on the reported range of phosphorus eliminated per day in stool and the range of stool mass per day in adults).

Not for clinical diagnostic purposes.

**Cauliflower IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Cauliflower, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


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**CBC with Differential, Blood**

**Clinical Information:** RBCs, WBCs, and platelets are produced in the bone marrow and released into the peripheral blood. The primary function of the RBC is to deliver oxygen to tissues. WBCs are key components of the immune system. Platelets play a vital role in blood clotting. Mean corpuscular volume (MCV) is a measure of the size of the average RBC. Anemias are characterized as microcytic (MCV <80), macrocytic (MCV >100), or normocytic. The red cell distribution width (RDW) is a measure of the degree of variation in RBC size (anisocytosis). RDW may be helpful in distinguishing between some anemias. For example, iron deficiency anemia is characterized by a high RDW, while thalassemia is characterized by a low RDW. These counts are used as clinical guides in the diagnosis or monitoring of many diseases.

**Useful For:** Screening tool to confirm a hematologic disorder, to establish or rule out a diagnosis, to detect an unsuspected hematologic disorder, or to monitor effects of radiation or chemotherapy

**Interpretation:** Results outside of normal value ranges may reflect a primary disorder of the cell-producing organs or an underlying disease. Results should be interpreted in conjunction with the patient's clinical picture and appropriate additional testing performed.

**Reference Values:**

### RED BLOOD CELL COUNT (RBC)

**Males:**
- 0-14 days: 4.10-5.55 x 10(12)/L
- 15 days-4 weeks: 3.16-4.63 x 10(12)/L
- 5 weeks-7 weeks: 3.02-4.22 x 10(12)/L
- 8 weeks-5 months: 3.43-4.80 x 10(12)/L
- 6 months-23 months: 4.03-5.07 x 10(12)/L
- 24 months-35 months: 3.89-4.97 x 10(12)/L
- 3-5 years: 4.00-5.10 x 10(12)/L
- 6-10 years: 4.10-5.20 x 10(12)/L
- 11-14 years: 4.20-5.30 x 10(12)/L
- 15-17 years: 4.30-5.30 x 10(12)/L
- Adults: 4.35-5.65 x 10(12)/L

**Females:**
- 0-14 days: 4.12-5.74 x 10(12)/L
- 15 days-4 weeks: 3.32-4.80 x 10(12)/L
- 5 weeks-7 weeks: 2.93-3.87 x 10(12)/L
- 8 weeks-5 months: 3.45-4.75 x 10(12)/L
- 6 months-23 months: 3.97-5.01 x 10(12)/L
- 24 months-35 months: 3.84-4.92 x 10(12)/L
- 3-5 years: 4.00-5.10 x 10(12)/L
- 6-10 years: 4.10-5.20 x 10(12)/L
11-14 years: 4.10-5.10 x 10^{12}/L
15-17 years: 3.80-5.00 x 10^{12}/L
Adults: 3.92-5.13 x 10^{12}/L

HEMOGLOBIN
Males:
0-14 days: 13.9-19.1 g/dL
15 days-4 weeks: 10.0-15.3 g/dL
5 weeks-7 weeks: 8.9-12.7 g/dL
8 weeks-5 months: 9.6-12.4 g/dL
6 months-23 months: 10.1-12.5 g/dL
24 months-35 months: 10.2-12.7 g/dL
3-5 years: 11.4-14.3 g/dL
6-8 years: 11.5-14.3 g/dL
9-10 years: 11.8-14.7 g/dL
11-14 years: 12.4-15.7 g/dL
15-17 years: 13.3-16.9 g/dL
Adults: 13.2-16.6 g/dL

Females:
0-14 days: 13.4-20.0 g/dL
15 days-4 weeks: 10.8-14.6 g/dL
5 weeks-7 weeks: 9.2-11.4 g/dL
8 weeks-5 months: 9.9-12.4 g/dL
6 months-35 months: 10.2-12.7 g/dL
3-5 years: 11.4-14.3 g/dL
6-8 years: 11.5-14.3 g/dL
9-10 years: 11.8-14.7 g/dL
11-17 years: 11.9-14.8 g/dL
Adults: 11.6-15.0 g/dL

HEMATOCRIT
Males:
0-14 days: 39.8-53.6%
15 days-4 weeks: 30.5-45.0%
5 weeks-7 weeks: 26.8-37.5%
8 weeks-5 months: 28.6-37.2%
6 months-23 months: 30.8-37.8%
24 months-35 months: 31.0-37.7%
3-7 years: 34-42%
8-11 years: 35-43%
12-15 years: 38-47%
16-17 years: 40-50%
Adults: 38.3-48.6%

Females:
0-14 days: 39.6-57.2%
15 days-4 weeks: 32.0-44.5%
5 weeks-7 weeks: 27.7-35.1%
8 weeks-5 months: 29.5-37.1%
6 months-23 months: 30.9-37.9%
24 months-35 months: 31.2-37.8%
3-7 years: 34-42%
8-17 years: 35-43%
Adults: 35.5-44.9%

MEAN CORPUSCULAR VOLUME (MCV)
Males:
### RED CELL DISTRIBUTION WIDTH (RDW)

#### Males:
- **0-14 days**: 14.8-17.0%
- **15 days-4 weeks**: 14.3-16.8%
- **5 weeks-7 weeks**: 13.8-16.1%
- **8 weeks-5 months**: 12.4-15.3%
- **6 months-23 months**: 12.9-15.6%
- **24 months-35 months**: 12.5-14.9%
- **3-5 years**: 11.3-13.4%
- **6-17 years**: 11.4-13.5%
- **Adults**: 11.8-14.5%

#### Females:
- **0-14 days**: 14.6-17.3%
- **15 days-4 weeks**: 14.3-16.2%
- **5 weeks-7 weeks**: 13.6-15.8%
- **8 weeks-5 months**: 12.2-14.3%
- **6 months-23 months**: 12.7-15.1%
- **24 months-35 months**: 12.4-14.9%
- **3-5 years**: 11.3-13.4%
- **6-17 years**: 11.4-13.5%
- **Adults**: 12.2-16.1%

### WHITE BLOOD CELL COUNT (WBC)

#### Males:
- **0-14 days**: 8.0-15.4 x 10^9/L
- **15 days-4 weeks**: 7.8-15.9 x 10^9/L
- **5 weeks-7 weeks**: 8.1-15.0 x 10^9/L
- **8 weeks-5 months**: 6.5-13.3 x 10^9/L
- **6 months-23 months**: 6.0-13.5 x 10^9/L
- **24 months-35 months**: 5.1-13.4 x 10^9/L
- **3-5 years**: 4.4-12.9 x 10^9/L
- **6-17 years**: 3.8-10.4 x 10^9/L

#### Females:
- **0-14 days**: 8.7-16.4 x 10^9/L
- **15 days-4 weeks**: 8.5-16.9 x 10^9/L
- **5 weeks-7 weeks**: 7.8-15.9 x 10^9/L
- **8 weeks-5 months**: 6.5-13.3 x 10^9/L
- **6 months-23 months**: 6.0-13.5 x 10^9/L
- **24 months-35 months**: 5.1-13.4 x 10^9/L
- **3-5 years**: 4.4-12.9 x 10^9/L
- **6-17 years**: 3.8-10.4 x 10^9/L
### Adults:

- **Platelets**
  - Males:
    - 0-14 days: 218-419 x 10^9/L
    - 15 days-4 weeks: 248-586 x 10^9/L
    - 5 weeks-7 weeks: 229-562 x 10^9/L
    - 8 weeks-5 months: 244-529 x 10^9/L
    - 6 months-23 months: 206-445 x 10^9/L
    - 24 months-35 months: 202-403 x 10^9/L
    - 3-5 years: 187-445 x 10^9/L
    - 6-9 years: 187-400 x 10^9/L
    - 10-13 years: 177-381 x 10^9/L
    - 14-17 years: 158-362 x 10^9/L
    - Adults: 135-317 x 10^9/L
  - Females:
    - 0-14 days: 144-449 x 10^9/L
    - 15 days-4 weeks: 279-571 x 10^9/L
    - 5 weeks-7 weeks: 331-597 x 10^9/L
    - 8 weeks-5 months: 247-580 x 10^9/L
    - 6 months-23 months: 214-459 x 10^9/L
    - 24 months-35 months: 189-394 x 10^9/L
    - 3-5 years: 187-445 x 10^9/L
    - 6-9 years: 187-400 x 10^9/L
    - 10-13 years: 177-381 x 10^9/L
    - 14-17 years: 158-362 x 10^9/L
    - Adults: 157-371 x 10^9/L

- **Neutrophils**
  - Males:
    - 0-14 days: 1.60-6.06 x 10^9/L
    - 15 days-4 weeks: 1.18-5.45 x 10^9/L
    - 5 weeks-7 weeks: 0.83-4.23 x 10^9/L
    - 8 weeks-5 months: 0.97-5.45 x 10^9/L
    - 6 months-23 months: 1.19-7.21 x 10^9/L
    - 24 months-35 months: 1.54-7.92 x 10^9/L
    - 3-5 years: 1.60-7.80 x 10^9/L
    - 6-16 years: 1.40-6.10 x 10^9/L
    - 17 years: 1.80-7.20 x 10^9/L
    - Adults: 1.56-6.45 x 10^9/L
  - Females:
    - 0-14 days: 1.73-6.75 x 10^9/L
    - 15 days-4 weeks: 1.23-4.80 x 10^9/L
    - 5 weeks-7 weeks: 1.00-4.68 x 10^9/L
    - 8 weeks-5 months: 1.04-7.20 x 10^9/L
LYMPHOCYTES
Males:
0-14 days: 2.07-7.53 x 10(9)/L
15 days-4 weeks: 2.11-8.38 x 10(9)/L
5 weeks-7 weeks: 2.47-7.95 x 10(9)/L
8 weeks-5 months: 2.45-8.89 x 10(9)/L
6 months-23 months: 1.56-7.83 x 10(9)/L
24 months-35 months: 1.13-5.52 x 10(9)/L
3-5 years: 1.60-5.30 x 10(9)/L
6-11 years: 1.40-3.90 x 10(9)/L
12-17 years: 1.00-3.20 x 10(9)/L
Adults: 0.95-3.07 x 10(9)/L

Females:
0-14 days: 1.75-8.00 x 10(9)/L
15 days-4 weeks: 2.42-8.20 x 10(9)/L
5 weeks-7 weeks: 2.29-9.14 x 10(9)/L
8 weeks-5 months: 2.14-8.99 x 10(9)/L
6 months-23 months: 1.52-8.09 x 10(9)/L
24 months-35 months: 1.25-5.77 x 10(9)/L
3-5 years: 1.60-5.30 x 10(9)/L
6-11 years: 1.40-3.90 x 10(9)/L
12-17 years: 1.00-3.20 x 10(9)/L
Adults: 0.95-3.07 x 10(9)/L

MONOCYTES
Males:
0-14 days: 0.52-1.77 x 10(9)/L
15 days-4 weeks: 0.28-1.38 x 10(9)/L
5 weeks-7 weeks: 0.28-1.05 x 10(9)/L
8 weeks-5 months: 0.28-1.07 x 10(9)/L
6 months-23 months: 0.25-1.15 x 10(9)/L
24 months-35 months: 0.19-0.94 x 10(9)/L
3-5 years: 0.30-0.90 x 10(9)/L
6-17 years: 0.20-0.80 x 10(9)/L
Adults: 0.26-0.81 x 10(9)/L

Females:
0-14 days: 0.57-1.72 x 10(9)/L
15 days-4 weeks: 0.42-1.21 x 10(9)/L
5 weeks-7 weeks: 0.28-1.21 x 10(9)/L
8 weeks-5 months: 0.24-1.17 x 10(9)/L
6 months-23 months: 0.26-1.08 x 10(9)/L
24 months-35 months: 0.24-0.92 x 10(9)/L
3-5 years: 0.30-0.90 x 10(9)/L
6-17 years: 0.20-0.80 x 10(9)/L
Adults: 0.26-0.81 x 10(9)/L

EOSINOPHILS
Males:
0-14 days: 0.12-0.66 x 10(9)/L
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Basophils (x 10⁹/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 days-4 weeks</td>
<td>0.08-0.80</td>
</tr>
<tr>
<td>5 weeks-7 weeks</td>
<td>0.05-0.57</td>
</tr>
<tr>
<td>8 weeks-5 months</td>
<td>0.03-0.61</td>
</tr>
<tr>
<td>6 months-23 months</td>
<td>0.02-0.82</td>
</tr>
<tr>
<td>24 months-35 months</td>
<td>0.03-0.53</td>
</tr>
<tr>
<td>3-11 years</td>
<td>0.00-0.50</td>
</tr>
<tr>
<td>12-17 years</td>
<td>0.10-0.20</td>
</tr>
<tr>
<td>Adults</td>
<td>0.03-0.48</td>
</tr>
</tbody>
</table>

**BASOPHILS**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Basophils (x 10⁹/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 days</td>
<td>0.09-0.64</td>
</tr>
<tr>
<td>15 days-4 weeks</td>
<td>0.06-0.75</td>
</tr>
<tr>
<td>5 weeks-7 weeks</td>
<td>0.04-0.63</td>
</tr>
<tr>
<td>8 weeks-5 months</td>
<td>0.02-0.74</td>
</tr>
<tr>
<td>6 months-23 months</td>
<td>0.02-0.58</td>
</tr>
<tr>
<td>24 months-35 months</td>
<td>0.03-0.46</td>
</tr>
<tr>
<td>3-11 years</td>
<td>0.00-0.50</td>
</tr>
<tr>
<td>12-17 years</td>
<td>0.10-0.20</td>
</tr>
<tr>
<td>Adults</td>
<td>0.03-0.48</td>
</tr>
</tbody>
</table>

**Clinical References:**

**CD10 Immunostain, Technical Component Only**

**Clinical Information:** CD10 is a cell surface glycoprotein present on bone marrow B precursors (hematogones) and myeloid cells (including neutrophils), follicle center B cells, and a subset of follicular T helper cells. CD10 is also expressed in the brush border of the upper part of the intestinal tract, bile canaliculi, kidney (glomerular and proximal tubular cells), pulmonary alveolar cells, myoepithelial cells of breast, prostate glandular cells, placental trophoblastic cells, endometrial stromal cells, some endothelial cells, and a minority of (myo-)fibroblasts (stromal cells). CD10 is most useful in the diagnosis of B-precursor-acute lymphoblastic leukemia, Burkitt lymphoma, and lymphomas of follicle cell center origin (follicular lymphoma, subset of large B-cell lymphomas).

**Useful For:** Phenotyping leukemias and lymphomas
Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


CD103 Immunostain, Technical Component Only

Clinical Information: CD103, also known as integrin alpha E, is an integrin subunit protein, which is widely expressed on T cells. CD103 is a useful diagnostic tool in the diagnosis of hairy cell leukemia.

Useful For: Aids in the diagnosis of hairy cell leukemia and marginal zone lymphomas

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


CD11c Immunostain, Technical Component Only

Clinical Information: CD11c is a member of the leukocyte specific integrin family, involved in adherence to activated endothelial cells and complement-mediated phagocytosis. CD11c is normally expressed on histiocytes and monocytes, and weakly expressed on granulocytes. CD11c is also expressed on certain B cell neoplasms, including hairy cell leukemia and splenic marginal zone lymphoma.
Useful For: Classification of B-cell neoplasms

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**CD123 Immunostain, Technical Component Only**

Clinical Information: In normal lymphoid tissues, CD123 is expressed in plasmacytoid monocytes and mast cells in interfollicular regions. In bone marrow, it is expressed in hematopoietic precursors, mast cells, and megakaryocytes. CD123 is part of the IL3 receptor complex, involved in cellular growth and differentiation. Certain reactive lymph nodes show increased numbers of plasmacytoid monocytes, eg, Kikuchi lymphadenitis. CD123 is characteristically expressed in blastic plasmacytoid dendritic cell neoplasm, aiding in its distinction from acute monocytic leukemia.

Useful For: Marker of plasmacytoid monocytes, mast cells, and megakaryocytes

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**CD13 Immunostain, Technical Component Only**

Clinical Information: CD13 plays roles in peptide metabolism (brush border membranes of small intestine, renal proximal tubules, and placenta), cell growth and differentiation, and phagocytosis. CD13 is normally expressed on myeloid lineage cells, including granulocytes and monocytes. It is also expressed on nonhematolymphoid cells including endothelial cells and fibroblasts, and present in a soluble form in plasma. This immunostain may be useful as a marker of myeloid lineage in acute leukemias.

Useful For: A marker of myeloid lineage

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation
CD138 70414

**CD138 (Syndecan) Immunostain, Technical Component Only**

**Clinical Information:** CD138 is expressed on plasma cells and can be useful in the diagnosis of plasma cell neoplasms. Epithelial cells and endothelial cells may also express CD138. In normal tonsil, CD138 strongly stains the membranes of mature plasma cells and squamous epithelial cells.

**Useful For:** Marker of plasma cells and squamous epithelial cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


CD14I 70375

**CD14 Immunostain, Technical Component Only**

**Clinical Information:** CD14 is a glycosylphosphatidylinositol (GPI)-linked glycoprotein that is preferentially expressed by mature cells of monocytic lineage (monocytes, macrophages, Langerhans cells) and on follicular dendritic cells. Lower levels of expression are observed on neutrophils. CD14 is important for the recognition and clearance of bacterial lipopolysaccharides and apoptotic cells. This immunostain may be useful as a marker of histiocytic and monocytic lineage in acute leukemias.

**Useful For:** A marker of histiocytic and monocytic lineage and follicular dendritic cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.
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**Clinical References:**

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**CD15 Immunostain, Technical Component Only**

**Clinical Information:** CD15 is expressed in granulocytes and can be expressed in malignant lymphomas and acute myeloid leukemias. The Reed-Sternberg cells of classical Hodgkin lymphoma are characteristically positive for CD15 and CD30.

**Useful For:** Phenotyping leukemias and lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD163 Immunostain, Technical Component Only**

**Clinical Information:** CD163 is a scavenger receptor for the hemoglobin-haptoglobin complex. CD163 is a marker of monocytic/histiocytic lineage, expressed late in maturation. It has superior specificity for monocytic/histiocytic lineage compared to CD68. In normal lymphoid tissues, staining of histiocytes in the paracortex and follicle center (tingible body macrophages) is seen. CD163 is usually negative in immature monocytic/histiocytic tumors (acute myeloid leukemia with monocytic differentiation).

**Useful For:** Identification of cells of monocytic/histiocytic lineage, expressed late in maturation

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are
verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**CD19 Immunostain, Bone Marrow, Technical Component Only**

**Clinical Information:** CD19 is expressed by normal and neoplastic B cells but is not expressed by T cells, monocytes, or granulocytes. CD19 protein appears early during B-cell maturation and is found during all stages of B-cell maturation, including plasma cells. CD19 is useful as an additional marker of B cell lineage in leukemias and lymphomas. Expression of CD19 may be seen in some acute myeloid leukemias.

**Useful For:** Identification of normal and neoplastic B cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**CD19 Immunostain, Technical Component Only**

**Clinical Information:** CD19 is expressed by normal and neoplastic B cells but is not expressed by T cells, monocytes, or granulocytes. CD19 protein appears early during B-cell maturation and is found during all stages of B-cell maturation, including plasma cells. CD19 is useful as an additional marker of B cell lineage in leukemias and lymphomas. Expression of CD19 may be seen in some acute myeloid leukemias.

**Useful For:** Identification of normal and neoplastic B cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a
**CD1a Immunostain, Technical Component Only**

**Clinical Information:** CD1a is a membrane surface glycoprotein that has good specificity for Langerhans cells and immature T cells. In normal skin, CD1a stains scattered Langerhans cells in the upper dermis and epidermis; reactivity in normal thymus gland is in the cortical thymocytes (immature T cells). This immunostain is useful in phenotyping acute lymphoblastic leukemia/lymphoma of T-cell lineage and in diagnosis of Langerhans cell histiocytosis.

**Useful For:** Marker of Langerhans cells and immature T cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD2 Immunostain, Bone Marrow, Technical Component Only**

**Clinical Information:** CD2 is a pan T-cell antigen, expressed on normal and neoplastic T cells and natural killer cells. In normal tonsil, the T cells predominate in interfollicular regions. CD2 immunostaining is useful in determining T-cell lineage in cases of T-cell lymphoma.

**Useful For:** Determining T-cell lineage

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
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Clinical Information: CD2 is a pan T-cell antigen, expressed on normal and neoplastic T cells and natural killer cells. In normal tonsil, the T cells predominate in interfollicular regions. CD2 immunostaining is useful in determining T-cell lineage in cases of T-cell lymphoma.

Useful For: Determining T-cell lineage

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CD20 Cell Expression Evaluation, Varies

Clinical Information: Monoclonal antibodies are critical tools for detecting cellular antigens in various hematologic diseases and are used to provide critical prognostic information (CD49d). Monoclonal antibodies are also used as therapeutic agents in a variety of hematologic diseases. For example: -Anti-CD20 (Rituxan): B-cell malignant lymphomas and multiple myeloma -Anti-CD52 (Campath-1H): B-cell chronic lymphocytic leukemia and T-cell disorders This list will undoubtedly expand over time to include other antibodies. It may be necessary to document expression of these markers by the malignant cells prior to initiating the respective monoclonal antibody therapy. Expression of these markers may also be required for follow-up to monitor the impact of treatment on residual normal counterparts (eg, CD20-positive lymphocytes in patients treated with anti-CD20). The distribution of these cellular antigens is well established in normal, reactive, and in various malignant disorders. The laboratory has several years of experience with therapeutic antibody monitoring of Mayo Clinic patients as part of the routine B-cell, T-cell, or acute immunophenotyping panels.

Useful For: Detecting cell-surface antigens on malignant cells that are potential therapeutic antibody targets, specifically CD20 Determining the eligibility of patients for monoclonal antibody therapies Monitoring response to the therapeutic antibody

Interpretation: The immunophenotyping report will summarize the pattern of antigenic expression on malignant cells and, if appropriate, the normal cellular counterparts that correspond to the therapeutic monoclonal antibody target.

Reference Values: Normal individuals have B lymphocytes, T lymphocytes, or myeloid cells that express the
corresponding cell-surface antigens in question.


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**CD20 Immunostain, Technical Component Only**

**Clinical Information:** CD20 is a phosphorylated protein preferentially expressed by mature B lymphocytes. CD20 is not expressed by most normal plasma cells. It is one of the most specific B-cell lineage-associated antigens used in the diagnosis of B-cell lymphomas.

**Useful For:** Classification of lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

recessive defect. Since these patients have normal numbers of B cells with absent CD19 expression on the cell surface, CD20 can be used as a marker to help identify these patients. A contrasting situation exists for patients receiving rituximab, ofatumumab, and other anti-CD20 monoclonal antibodies that are used to treat certain cancers, autoimmune diseases, or for B-cell depletion to prevent humoral rejection in positive crossmatch renal transplantation. These agents block available CD20-binding sites and, therefore, the antibody used for this flow cytometric assay cannot recognize the CD20 molecule on B cells. The concomitant use of the CD19 marker provides information on the extent of B-cell depletion when using this particular treatment strategy. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer cell counts, on the other hand, are constant throughout the day. Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration. In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells. It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening, and during summer compared to winter. These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

Useful For: Evaluation of CD19 deficiency in patients with a suspected CD19 deficiency (humoral immunodeficiency) Confirming complete absence of B cells in suspected primary humoral immunodeficiencies using both CD19 and CD20 markers Assessing therapeutic B-cell depletion quantitatively (absolute counts of cells/mcL) in any clinical context, including malignancies, autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and membranous glomerulonephritis among others, and treatment or prevention of acute humoral rejection in positive crossmatch renal transplant recipients This test is not useful for assessing whether B cells express the target molecule (CD20) in the context of initiating therapeutic monoclonal anti-CD20 antibody therapy (rituximab, ofatumumab, and tositumomab) for any of the hematological malignancies, or in other clinical contexts, such as autoimmunity, instead order CEE20 / CD20 Cell Expression Evaluation.

Interpretation: The presence of CD20+ B cells with corresponding absence of CD19 staining in individuals not receiving anti-CD20 monoclonal antibody treatment or with clinical features of variable primary humoral immunodeficiency may suggest an underlying CD19 deficiency, which should be further evaluated. Absence of both CD20 and CD19 markers on B cells in blood from individuals not on anti-CD20 monoclonal antibody treatment is consistent with complete mature and immature peripheral B-cell depletion, which may be due to an underlying primary immunodeficiency. Patients receiving B-cell depleting therapy with anti-CD20 antibodies can show unusual populations of B cells on reconstitution that express either CD19 or CD20 due to a phenomenon known as trogocytosis.

Reference Values:

<table>
<thead>
<tr>
<th>%CD19 B CELLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; or =19 years: 4.6-22.1%</td>
</tr>
</tbody>
</table>

CD19 ABSOLUTE
> or =19 years: 56.6-417.4 cells/mcL

<table>
<thead>
<tr>
<th>%CD20 B CELLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; or =19 years: 5.0-22.3%</td>
</tr>
</tbody>
</table>

CD20 ABSOLUTE
> or =19 years: 74.4-441.1 cells/mcL

CD45 ABSOLUTE
18-55 years: 0.99-3.15 thou/mcL
>55 years: 1.00-3.33 thou/mcL

CD21 Immunostain, Technical Component Only

**Clinical Information:** CD21 strongly stains the cytoplasm and membranes of the follicular dendritic cells and the membranes of a subset of the mantle zone lymphocytes. Follicular dendritic cells form a basket-weave meshwork in the germinal centers of lymphoid follicles, where they present antigens to B cells. Diagnostically, CD21 may be useful to support a diagnosis of follicular dendritic cell sarcoma, or to confirm the presence of lymphoid follicles.

**Useful For:** Identification of follicular dendritic cells and a subset of mantle zone lymphocytes

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

CD22 Immunostain, Technical Component Only

**Clinical Information:** CD22 is expressed on B lymphocytes. It can be used as an alternative B-cell marker to CD20 or CD79a. Diagnostically, CD22 is useful to confirm B-cell lineage in malignant lymphomas.

**Useful For:** Determining B-cell lineage

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

CD23 Immunostain, Technical Component Only

Clinical Information: CD23 strongly stains the cytoplasm and membranes of follicular dendritic cells and the membranes of a subset of follicular mantle zone B-lymphocytes. Typically, B-cell small lymphocytic lymphoma/chronic lymphocytic leukemias are CD5 positive and CD23 positive, while mantle cell lymphoma is CD5 positive and CD23 negative. Antibodies to CD23 are diagnostically useful in the classification of low-grade B-cell lymphomas.

Useful For: Identification of follicular dendritic cells Classification of low-grade B-cell lymphomas

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

CD25 Immunostain, Technical Component Only

Clinical Information: CD25 is the receptor for IL2 and is expressed on activated T cells, B cells, and macrophages. It will stain only scattered cells in normal tonsil. CD25 is expressed in certain types of B-cell lymphoma (hairy cell leukemia) and T-cell lymphoma (adult T-cell lymphoma/leukemia [ATLL]). An anti-CD25 therapy can be used in patients who have lymphomas that express CD25.

Useful For: Classification of lymphomas
**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC/Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**CD273**

**CD273 (PD-L2) Immunostain, Technical Component Only**

**Clinical Information:** CD273 also known as programmed cell death 1-ligand 2 (PD-L2) regulates T-cell activation in addition to immune responses and is a member of the B7 family of cell surface ligands. CD273 expression is a specific marker of primary mediastinal large B-cell lymphoma (PMLBL) and it can be used to distinguish PMLBL from diffuse large B-cell lymphoma, not otherwise specified (DLBCL-NOS), which occurs in the mediastinum. These 2 entities have distinct clinical behavior and respond uniquely to differently therapies.

**Useful For:** Differentiation of primary mediastinal large B-cell lymphoma (PMLBL) from diffuse large B cell-lymphoma (DLBCL)

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist is required order PATHC/Pathology Consultation. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**CD279**

**CD279 (PD-1) Immunostain, Technical Component Only**

**Clinical Information:** CD279 (PD-1) is an immunoregulatory receptor highly expressed by follicular T helper cells, and its expression has also been shown in the neoplastic counterpart of this T-cell subset, angioimmunoblastic T-cell lymphoma. This molecule interacts with PD-L1 (B7H1) expressed on follicular dendritic cells and other cell types, which serves to attenuate T-cell activation. In the appropriate histologic context, a background rich in CD279-positive T cells can support a diagnosis of nodular lymphocyte-predominant Hodgkin lymphoma.

**Useful For:** Identification of follicular T helper cells and phenotyping of angioimmunoblastic T-cell
Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Reference Values:
N/A


CD3 Immunostain, Technical Component Only

Clinical Information: CD3 is part of the T-cell antigen receptor complex found on the surface of T lymphocytes. In paraffin sections, antibodies to CD3 will also react with a subset of natural killer cells that express the cytoplasmic epsilon chain of CD3. In normal tonsil, the T cells predominate in the interfollicular regions. Diagnostically, antibodies to CD3 are useful in demonstrating T-cell lineage of malignant lymphomas.

Useful For: Demonstrating T-cell lineage

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


CD30 Immunostain, Technical Component Only

Clinical Information: CD30 is a member of the tumor necrosis factor receptor (TNF-R)
superfamily. Expression of CD30 can also be seen in embryonal carcinomas, malignant melanomas, mesenchymal tumors, and activated T and B lymphocytes and plasma cells. Reed-Sternberg cells of classical Hodgkin lymphoma, as well as the neoplastic cells of anaplastic large cell lymphoma express CD30.

**Useful For:** Identification of CD30 expression in a variety of neoplasms

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**CD31 Immunostain, Technical Component Only**

**Clinical Information:** CD31 is expressed on endothelial cells, showing some membrane and occasional cytoplasmic staining. It is not expressed on discontinuous endothelium (eg, splenic red pulp). It is also expressed on megakaryocytes, histiocytes, plasma cells, and T-cell subsets. Tonsil sections will exhibit endothelial positivity in vessels primarily located in connective tissue areas around follicles and near the epithelial borders. Diagnostically, CD31 expression can confirm a diagnosis of angiosarcoma, a neoplasm of endothelial cells.

**Useful For:** Marker of endothelial cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**CD33 Immunostain, Technical Component Only**

**Clinical Information:** CD33 is a transmembrane protein that is a member of the sialic acid-binding immunoglobulin-like lactic (Siglec) family. The exact function of CD33 is not known, but it may be involved in cell to cell adhesion. It is not expressed on hematopoietic stem cells, but is expressed on maturing myelomonocytic cells. As granulocytes mature, there is progressive down regulation of CD33. Monocytes and macrophage/histiocytic cells maintain strong expression of CD33. In normal bone marrow, weak to moderate CD33 staining is seen on granulocytic and monocytic precursors, with strong staining in scattered mast cells. CD33 staining is useful for diagnosis of myeloid neoplasms and classification of acute leukemias. A therapeutic antibody targeting CD33 (gemtuzumab/Myelotarg) is available.

**Useful For:** Classification of myeloid neoplasms and acute leukemias

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD34 Immunostain, Technical Component Only**

**Clinical Information:** CD34 is an 115-kD membrane-associated antigen found on human hematopoietic progenitor cells and vascular endothelial cells. In normal tonsil sections, antibodies to CD34 strongly stain vascular endothelial cells. Diagnostically, CD34 is used as a marker of immaturity in the setting of acute myeloid leukemia or B cell lymphoblastic leukemia. It is also useful in the classification of spindle cell neoplasms (gastrointestinal stromal tumors, solitary fibrous tumors, and angiosarcomas are often positive).

**Useful For:** A marker of hematopoietic progenitor cells and vascular endothelial cells Classification of spindle cell neoplasms

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
CD35 Immunostain, Technical Component Only

**Clinical Information:** CD35 stains the membrane and cytoplasm of follicular dendritic cells and granulocytes. Follicular dendritic cells form a basketweave meshwork in the germinal centers of lymphoid follicles, where they present antigens to B cells. CD35 is useful in the diagnosis of follicular dendritic-cell sarcoma.

**Useful For:** Identification of follicular dendritic cells and granulocytes

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

CD38 Immunostain, Technical Component Only

**Clinical Information:** CD38 is a transmembrane protein that shows enzymatic activity involved in the production of calcium-mobilizing compounds and receptor activity involved in cellular adhesion and signaling in leukocytes. It is expressed in a variety of cell types including hematopoietic precursors, plasma cells, germinal center B cells (weakly), a subset of T and natural killer cells, erythrocytes, platelets, prostatic epithelium, and smooth and striated muscle cells. In some cases it may be a marker of activation. CD38 expression may be useful in the diagnosis of lymphoproliferative and plasma cell proliferative disorders. Determination of CD38 expression by flow cytometry has been used as a prognostic marker on chronic lymphocytic leukemia.

**Useful For:** Classification of lymphoproliferative and plasma cell proliferative disorders

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in
CD4 Count for Immune Monitoring, Blood

Clinical Information: Lymphocytes in peripheral blood (circulation) are heterogeneous and can be broadly classified into T cells, B cells, and natural killer cells. There are various subsets of each of these individual populations with specific cell-surface markers and function. This assay provides absolute (cells/mL) and relative (%) quantitation for total T cells and CD4+ and CD8+ T-cell subsets, in addition to a total lymphocyte count (CD45+). Each of these lymphocyte subpopulations have distinct effector and regulatory functions and are maintained in homeostasis under normal physiological conditions. Each of these lymphocyte subsets can be identified by a combination of 1 or more cell surface markers. The CD3 antigen is a pan-T cell marker, and T cells can be further divided into 2 broad categories, based on the expression of CD4 or CD8 co-receptors. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells increase between 8:30 a.m. and noon with no change between noon and afternoon.(1) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(2-4) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(2) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared to the evening(5) and during summer compared to winter.(6) These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets. Abnormalities in the number and percent of CD3, CD4, and CD8 T cells have been described in a number of different disease conditions. In patients who are infected with HIV, the CD4 count is measured for AIDS diagnosis and for initiation of antiviral therapy. The progressive loss of CD4 T-lymphocytes in patients infected with HIV is associated with increased infections and complications. The Public Health Service has recommended that all HIV-positive patients be tested every 3 to 6 months for the level of CD4 T-lymphocytes. Basic T-cell subset quantitation is also very useful in the evaluation of patients with primary cellular immunodeficiencies of all ages, including follow-up for newborn screening for severe combined immunodeficiency and immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, or any other relevant clinical condition where immunomodulatory treatment is used, and the T-cell compartment is specifically affected. It is also helpful as a preliminary screening assay for gross quantitative anomalies in T cells, whether related to malignancies or infection.

Useful For: Serial monitoring of CD4 T cell count in HIV-positive patients Useful for follow-up and diagnostic evaluation of primary cellular immunodeficiencies, including severe combined immunodeficiency T-cell immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, and other immunological conditions where such treatment is utilized Assessment of T-cell immune reconstitution post hematopoietic cell transplantation Early screening of gross quantitative anomalies in T cells in infection or malignancies

Interpretation: HIV treatment guidelines from the US Department of Health and Human Services and the International Antiviral Society USA Panel recommend antiviral treatment in all patients with HIV infection, regardless of CD4 T-cell count.(7,8) Additionally, antibiotic prophylaxis for Pneumocystis jiroveci infection and other opportunistic infections is recommended for patients with CD4 counts below 200 cells/mL.

Reference Values: The appropriate age-related reference values will be provided on the report.

CD4 Count for Monitoring, New York, Blood

Clinical Information: Lymphocytes in peripheral blood (circulation) are heterogeneous and can be broadly classified into T cells, B cells, and natural killer (NK) cells. There are various subsets of each of these individual populations with specific cell-surface markers and function. This assay provides absolute (cells/mL) and relative (%) quantitation for total T cells and CD4+ and CD8+ T-cell subsets, in addition to a total lymphocyte count (CD45+). Each of these lymphocyte subpopulations have distinct effector and regulatory functions and are maintained in homeostasis under normal physiological conditions. Each of these lymphocyte subsets can be identified by a combination of 1 or more cell surface markers. The CD3 antigen is a pan T-cell marker, and T cells can be further divided into 2 broad categories, based on the expression of CD4 or CD8 coreceptors. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells increase between 8:30 a.m. and noon with no change between noon and afternoon. (1) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration. (2-4) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells. (2) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared to the evening and during summer compared to winter. (6) These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets. Abnormalities in the number and percent of CD3, CD4, and CD8 T cells have been described in a number of different disease conditions. In patients who are infected with HIV, the CD4 count is measured for AIDS diagnosis and for initiation of antiviral therapy. The progressive loss of CD4 T lymphocytes in patients infected with HIV is associated with increased infections and complications. The Public Health Service has recommended that all HIV-positive patients be tested every 3 to 6 months for the level of CD4 T lymphocytes. Basic T-cell subset quantitation is also very useful in the evaluation of patients with primary cellular immunodeficiencies of all ages, including follow-up for newborn screening for severe combined immunodeficiency and immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, or any other relevant clinical condition where immunomodulatory treatment is used, and the T-cell compartment is specifically affected. It is also helpful as a preliminary screening assay for gross quantitative anomalies in T cells, whether related to malignancies or infection.

Useful For: Serial monitoring of CD4 T-cell count in HIV-positive patients Follow-up and diagnostic evaluation of primary cellular immunodeficiencies, including severe combined immunodeficiency T-cell immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, and other immunological conditions where such treatment is utilized Assessment of T-cell immune reconstitution post hematopoietic cell transplantation Early screening of gross quantitative anomalies in T cells in infection or malignancies

Interpretation: HIV treatment guidelines from the US Department of Health and Human Services and
the International Antiviral Society-USA Panel recommend antiviral treatment in all patients with HIV infection, regardless of CD4 T-cell count. Additionally, antibiotic prophylaxis for Pneumocystis jiroveci infection and other opportunistic infections is recommended for patients with a CD4 count below 200 cells/mL.

Reference Values:
The appropriate age-related reference values will be provided on the report.

Clinical References:

CD4 Immunostain, Technical Component Only

Clinical Information: CD4 is expressed on a subset of T cells (T helper cells), histiocytes, and monocytes. In normal tonsil, the T cells predominate in interfollicular regions. This immunostain is also used to support T cell or histiocytic lineage in hematolymphoid neoplasms.

Useful For: Identification of T helper cells, histiocytes, and monocytes

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:
to form the peripheral T-cell repertoire. There is a decrease in naive T cells derived from the thymus with age due to age-related decline in thymic output. Recent thymic emigrants (RTEs) typically refers to those populations of naive T cells that have not diluted their TREC copies (T-cell receptor excision circles) by homeostatic or antigen-driven cell division. Naive T cells can be long-lived in the periphery and postpuberty, and in adults, peripheral T-cell homeostasis is maintained by a balance of thymic output and peripheral T-cell expansion and this proportion changes with age. In infants and prepubertal children, the T-cell repertoire is largely maintained by thymic-derived naive T cells. RTEs express TREC indicative of naive T cells derived from the thymus.(1) In the CD4 T-cell compartment it has been shown that naive CD45RA+ T cells coexpressing CD31 had a higher frequency of TREC compared to T cells lacking CD31.(2) The higher proportion of TREC+ naive T cells indicate a more recent thymic ontogeny since TREC can be diluted by cell division (since they are extrachromosomal). It has been shown that CD31+CD4+ T cells continue to possess a relatively higher proportion of TREC despite an age-related 10-fold reduction after the neonatal period.(3) CD4 RTEs (CD31+CD4+CD45RA+) have longer telomeres and higher telomerase activity, which, along with the increased frequency of TREC positivity suggests a population of T cells with low replicative history.(3) The same study has also shown that CD31+ CD4+ T cells are an appropriate cell population to evaluate thymic reconstitution in lymphopenic children posthematopoietic cell transplant.(3) A Mayo study (unpublished) shows that the CD31 marker correlates with TREC-enriched T cells across the spectrum of age and correlates with thymic recovery in adults after autologous hematopoietic cell transplantation.(4) CD31+ CD4 RTEs have also been used to evaluate T-cell homeostatic anomalies in patients with relapsing-remitting multiple sclerosis.(5) For patients with DiGeorge syndrome (DGS)—a cellular immunodeficiency associated with other congenital problems including cardiac defects, facial dysmorphism, hypoparathyroidism, and secondary hypocalcemia, and chromosome 22q11.2 deletion (in a significant proportion of patients)—measurement of thymic function provides valuable information on the functional phenotype, ie, complete DGS (associated with thymic aplasia in a minority of patients) or partial DGS (generally well-preserved thymic function seen the in the majority of patients). Thymus transplants have been performed in patients with complete DGS, but are typically not required in partial DGS. There can be change in peripheral T-cell counts in DGS patients with age.

**Useful For:** Evaluating thymic reconstitution in patients following hematopoietic cell transplantation, chemotherapy, immunomodulatory therapy, and immunosuppression Evaluating thymic recovery in HIV-positive patients on highly active antiretroviral therapy Evaluating thymic output in patients with DiGeorge syndrome or other cellular immunodeficiencies Assessing the naive T-cell compartment in a variety of immunological contexts (autoimmunity, cancer, immunodeficiency, and transplantation) Identification of thymic remnants postthymectomy for malignant thymoma or as an indicator of relapse of disease (malignant thymoma) or other contexts of thymectomy

**Interpretation:** The absence or reduction of CD31+CD4 recent thymic emigrants (RTEs) generally correlates with loss or reduced thymic output and changes in the naive CD4 T-cell compartment, especially in infancy and prepubertal children. The CD4RTE result has to be interpreted more cautiously in adults due to age-related decline in thymic function and correlated with total CD4 T cell count and other relevant immunological data. CD4 RTEs measured along with TREC (TREC / T-Cell Receptor Excision Circles (TREC) Analysis, Blood) provides a comprehensive assessment of thymopoiesis, but should not be used in adults over the sixth decade of life as clinically meaningful information on thymic function is limited in the older population due to a physiological decline in thymic activity. To evaluate immune reconstitution or recovery of thymopoiesis post-T-cell depletion due to posthematopoietic cell transplant, immunotherapy, or other clinical conditions, it is helpful to systematically (serially) measure CD4RTE, and TREC copies in the appropriate age groups.

**Reference Values:**

**CD4 ABSOLUTE**

**Males**

- 1 month-17 years: 153-1,745 cells/mcL
- 18-70 years: 290-1,175 cells/mcL

Reference values have not been established for patients that are <30 days of age.

Reference values have not been established for patients that are >70 years of age.

**Females**

- 1 month-17 years: 582-1,630 cells/mcL
- 18-70 years: 457-1,766 cells/mcL

Reference values have not been established for patients that are <30 days of age.

Reference values have not been established for patients that are >70 years of age.
Reference values have not been established for patients that are <30 days of age. Reference values have not been established for patients that are >70 years of age.

CD4 RTE %
Males
- 1 month-17 years: 19.4-60.9%
- 18-25 years: 6.4-51.0%
- 26-55 years: 6.4-41.7%
- > or =56 years: 6.4-27.7%
Reference values have not been established for patients that are <30 days of age. Reference values have not been established for patients that are >70 years of age.

Females
- 1 month-17 years: 25.8-68.0%
- 18-25 years: 6.4-51.0%
- 26-55 years: 6.4-41.7%
- > or =56 years: 6.4-27.7%
Reference values have not been established for patients that are <30 days of age. Reference values have not been established for patients that are >70 years of age.

CD4 RTE ABSOLUTE
Males
- 1 month-17 years: 50.0-926.0 cells/mcL
- 18-70 years: 42.0-399.0 cells/mcL
Reference values have not been established for patients that are <30 days of age. Reference values have not been established for patients that are >70 years of age.

Females
- 1 month-17 years: 170.0-1,007.0 cells/mcL
- 18-70 years: 42.0-832.0 cells/mcL
Reference values have not been established for patients that are <30 days of age. Reference values have not been established for patients that are >70 years of age.

Clinical References:

CD43 Immunostain, Technical Component Only

Clinical Information: CD43 is expressed by normal T lymphocytes, granulocytes, and granulocyte precursors, monocytes, macrophages, plasma cells, and megakaryocytes. In normal tonsil, CD43 will mainly show staining in T lymphocytes and plasma cells in interfollicular areas.

Useful For: Identification of T lymphocytes, monocytes, macrophages, granulocytes, plasma cells, and a subset of B lymphocytes

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation,
CD45 Leukocyte Common Antigen (LCA) Immunostain, Technical Component Only

**Clinical Information:** CD45 is also called leukocyte common antigen given its shared expression in the vast majority of cells of hematolymphoid lineage. The CD45 antibody used is a cocktail of 2 clones, PD7/26 (detects the CD45RB isoform), and 2B11 (detects a common CD45 protein). CD45 expression is very specific and quite sensitive for cells of hematolymphoid lineage, thus, distinguishing lymphoma/leukemia from other neoplasms. The main exception is classical Hodgkin Lymphoma, in which CD45 expression is absent.

**Useful For:** Aids in distinguishing lymphoma/leukemia from other neoplasms

**Interpretation:** The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
laboratory has several years of experience with therapeutic antibody monitoring of Mayo Clinic patients as part of the routine B-cell, T-cell, or acute immunophenotyping panels.

**Useful For:** Detecting cell-surface antigens on malignant cells that are potential therapeutic antibody targets, specifically CD49d Determining the eligibility of patients for monoclonal antibody therapies Monitoring response to the therapeutic antibody

**Interpretation:** The immunophenotyping report will summarize the pattern of antigenic expression on malignant cells and, if appropriate, the normal cellular counterparts that correspond to the therapeutic monoclonal antibody target.

**Reference Values:**
Normal individuals have B lymphocytes, T lymphocytes, or myeloid cells that express the corresponding cell-surface antigens in question.

**Clinical References:**

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**CD5 Immunostain, Technical Component Only**

**Clinical Information:** CD5 is expressed normally on all T cells (one of the pan T-cell antigens). It can be aberrantly expressed by B-cell lymphomas (most commonly mantle cell lymphoma, B-cell small lymphocytic lymphoma). Expression of CD5 is useful to support T-cell lineage in T-cell lymphomas, or to help subclassify B-cell lymphomas.

**Useful For:** Marker of T-cell lineage Phenotyping B-cell lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD52 Cell Expression Evaluation, Varies**

**Clinical Information:** Monoclonal antibodies are critical tools for detecting cellular antigens in
various hematologic diseases and are used to provide critical prognostic information (CD49d). Monoclonal antibodies are also used as therapeutic agents in a variety of hematologic diseases. For example: -Anti-CD20 (Rituxan): B-cell malignant lymphomas and multiple myeloma -Anti-CD52 (Campath-1H): B-cell chronic lymphocytic leukemia and T-cell disorders This list will undoubtedly expand over time to include other antibodies. It may be necessary to document expression of these markers by the malignant cells prior to initiating the respective monoclonal antibody therapy. Expression of these markers may also be required for follow-up to monitor the impact of treatment on residual normal counterparts (eg, CD20-positive lymphocytes in patients treated with anti-CD20). The distribution of these cellular antigens is well established in normal, reactive, and in various malignant disorders. The laboratory has several years of experience with therapeutic antibody monitoring of Mayo Clinic patients as part of the routine B-cell, T-cell, or acute immunophenotyping panels.

**Useful For:** Detecting cell-surface antigens on malignant cells that are potential therapeutic antibody targets, specifically CD52 Determining the eligibility of patients for monoclonal antibody therapies Monitoring response to the therapeutic antibody

**Interpretation:** The immunophenotyping report will summarize the pattern of antigenic expression on malignant cells and, if appropriate, the normal cellular counterparts that correspond to the therapeutic monoclonal antibody target.

**Reference Values:**
Normal individuals have B lymphocytes, T lymphocytes, or myeloid cells that express the corresponding cell-surface antigens in question.

**Clinical References:**

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**CD56 Immunostain, Technical Component Only**

**Clinical Information:** CD56 is an adhesion molecule mediating homophilic and heterophilic adhesion in neurons, natural killer cells, and a small subset of CD4- and CD8-positive T cells. It is expressed in tumors with neuroendocrine differentiation (small cell lung carcinoma and neural-derived tumors) or natural killer cell lineage (subset of lymphomas). In normal small intestine, the ganglion cells in the muscle wall and nerves will show strong staining. Scattered lymphocytes may also be positive.

**Useful For:** Aids in the identification of tumors with neuroendocrine differentiation Aids in the identification of natural killer cell lineage in a subset of lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
CD57 Immunostain, Technical Component Only

**Clinical Information:** CD57 is a 110-kD glycoprotein that is selectively expressed on natural killer cells and a subset of follicular T helper cells. Antibodies to CD57 also stain the myelin sheaths of central and peripheral nervous system cells. In normal tonsil, CD57 will stain a minor population of lymphocytes in the germinal centers. It is immunoreactive in tumors of neuroectodermal origins such as small cell carcinoma of the lung and carcinoid tumors, and is positive in adenocarcinomas of the prostate as well as normal and hyperplastic prostatic epithelium. Increased numbers of CD57-positive T cells are present in the background of lymphocyte-predominant Hodgkin lymphoma.

**Useful For:** Marker of natural killer cells and a subset of follicular T helper cells Aids in the identification of tumors of neuroectodermal origin

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


CDKP1 70486 CD68 (KP1) Immunostain, Technical Component Only

Clinical Information: In normal tissues, CD68 KP-1 stains the cytoplasm of the granulocytes and myeloid progenitors in the bone marrow, monocytes, and macrophages, and osteoclasts. KP-1 reacts against a carbohydrate moiety of CD68. Although CD68 KP-1 is primarily used as a histiocytic marker, it is not specific for histiocytes. It can also be expressed in malignant melanoma, granular cell tumors, peripheral nerve sheath tumors, malignant fibrous histiocytoma, and other mesenchymal neoplasms and rare carcinomas.

Useful For: Aids in the identification of histiocytic and myeloid lineage cells

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD68 (PG-M1) Immunostain, Technical Component Only**

**Clinical Information:** In normal tissues, CD68 PG-M1 stains monocytes and macrophages and, to a lesser extent, neutrophils in a cytoplasmic granular staining pattern. It has greater specificity for monocytes and macrophages than does KP-1, but its immunohistochemical staining pattern in nonhematolymphoid tumors has not been studied as extensively as CD68 KP-1. Diagnostically, CD68 PG-M1 is usually applied to cases of acute leukemia to demonstrate monocytic differentiation and to cases of hematolymphoid neoplasms that are suspected to represent histiocytic sarcomas.

**Useful For:**
- Aids in the identification of monocytic differentiation
- Aids in phenotyping hematolymphoid neoplasms that are suspected to represent histiocytic sarcomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD7 Immunostain, Technical Component Only**

**Clinical Information:**

**Useful For:**
- Aids in the identification of monocytic differentiation
- Aids in phenotyping hematolymphoid neoplasms that are suspected to represent histiocytic sarcomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
**Clinical Information:** CD7 is expressed normally on all T cells (one of the pan T-cell antigens) and natural killer cells. Expression of CD7 can be aberrantly lost in T-cell lymphomas, providing support for a diagnosis of T-cell lymphoma. In normal tonsil, the T cells predominate in interfollicular regions.

**Useful For:** Aids in the identification of T cells and natural killer cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD71 Immunostain, Technical Component Only**

**Clinical Information:** The transferrin receptor (CD71) is highly expressed on the surface of cells of the erythroid lineage and mediates the uptake of transferrin-iron complexes. Transferrin receptor expression levels are highest in early erythroid precursors through the intermediate normoblast phase, then expression decreases through the reticulocyte phase.

**Useful For:** Assessment of erythroid lineage

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CD79a Immunostain, Technical Component Only**

**Clinical Information:** CD79a stains the cytoplasm and membrane of B lymphocytes and megakaryocytes. CD79a is a protein expressed on the surface of B lymphocytes at all stages of maturation, from B-lymphocyte precursors through plasma cells. Its function is to transduce the signal of
antigen binding to immunoglobulin into the cytoplasm of the B lymphocyte initiating intracellular signaling. Antibodies to CD79a are diagnostically useful to demonstrate B cell lineage of acute lymphoblastic leukemia, malignant lymphomas and chronic lymphoproliferative disorders.

**Useful For:** Phenotyping leukemias and lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**CD8 Immunostain, Technical Component Only**

**Clinical Information:** CD8 is expressed in a subset of T cells (cytotoxic T cells). It appears on the surface of cytotoxic T lymphocytes during intrathymic maturation and is present on approximately 20% of the T cells in the peripheral blood, lymph nodes, and spleen.

**Useful For:** Aids in the identification of cytotoxic T cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**CD8 T-Cell Immune Competence Panel, Global**

**Clinical Information:** CD8 T cells play an important role in the immune response to viral or intracellular infectious agents, as well as antitumor immunity and immune surveillance. Upon
activation, CD8 T cells mediate a variety of effector functions, including cytokine secretion and cytotoxicity. Interferon-gamma (IFN-gamma) is one of the early cytokines produced by CD8 T cells; it is released within a few hours of activation. The cytotoxic function is mediated by the contents of the cytolytic granules. Cell-surface mobilization of the cytolytic granule components, CD107a and CD107b, also known as lysosome-associated membrane proteins LAMP-1 and LAMP-2, occurs when CD8 T cells mediate their cytolytic function and degranulate. CD8 T-cell activation occurs either through the T cell receptor peptide major histocompatibility complex (MHC) or by use of a mitogen (eg, phorbol myristate acetate and the calcium ionophore ionomycin). Mitogen-mediated activation is antigen nonspecific. Impairment of global CD8 T-cell activation (due to inherent cellular immunodeficiency or as a consequence of over-immunosuppression by therapeutic agents) results in reduced production of IFN-gamma and other cytokines, reduced cytotoxic function, and increased risk for developing infectious complications. Agents associated with over-immunosuppression include the calcineurin inhibitors (eg, cyclosporine A, FK506 [Prograf/tacrolimus], and rapamycin [sirolimus]), antimetabolites (eg, mycophenolate mofetil), and thymoglobulin. Immunosuppression is most commonly used for allograft maintenance in solid-organ transplant recipients, to prevent graft-versus-host disease in allogeneic hematopoietic stem cell transplant patients and, to treat patients with autoimmune diseases. In these settings, reducing the risk for developing infectious complications as a result of over-immunosuppression is a clinical challenge. Therapeutic drug monitoring is routinely used in the transplant practice to avoid overtreatment and to determine patient compliance. But, the levels of drugs measured in blood do not directly correlate with the administered dose due to individual pharmacokinetic differences. Furthermore, drug levels may not necessarily correlate with biological activity of the drug. Consequently, it may be beneficial to consider modification of the immunosuppression regimen based on the patient's level of functional immune competence. This assay provides a means to evaluate over-immunosuppression within the CD8 T-cell compartment (global CD8 T-cell function). Intracellular IFN-gamma expression is a marker for CD8 T-cell activation. Surface CD107a and CD107b are markers for cytotoxic function. This test may be most useful when ordered at the end of induction immunosuppression and 2 to 3 months after maintenance immunosuppression to ensure that global CD8 T-cell function is not compromised. The test may also provide value when immunosuppression is increased to halt or prevent graft rejection, to provide information on a balance between over-immunosuppression with subsequent infectious comorbidities and, under-immunosuppression with resultant graft rejection. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8.30 a.m. and noon with no change between noon and afternoon. Natural killer-cell counts, on the other hand, are constant throughout the day. Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration. In fact, cortisol and catecholamine concentrations control distribution and therefore, numbers of naive versus effector CD4 and CD8 T cells. It is generally accepted that lower CD4 T-cell counts are seen in the morning compared to the evening and during summer compared to winter. These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

**Useful For:** Determining over immunosuppression within the CD8 T-cell compartment, when used on transplant recipients and patients with autoimmune disorders receiving therapy with immunosuppressant agents

**Interpretation:** Interferon-gamma (IFN-gamma) and CD107a and CD107b expression below the defined reference range are consistent with a global impairment in CD8 T-cell function, most likely due to over immunosuppression. IFN-gamma and CD107a and CD107b levels greater than the defined reference range are unlikely to have any clinical significance.

**Reference Values:**
The appropriate age-related reference values will be provided on the report.


**GLIC 89317**

**CD8 T-Cell Immune Competence, Global, Blood**

**Clinical Information:** CD8 T cells play an important role in the immune response to viral or intracellular infectious agents, as well as antitumor immunity and immune surveillance. Upon activation, CD8 T cells mediate a variety of effector functions, including cytokine secretion and cytotoxicity. Interferon-gamma (IFN-gamma) is one of the early cytokines produced by CD8 T cells; it is released within a few hours of activation.(1) The cytotoxic function is mediated by the contents of the cytolytic granules.(1) Cell-surface mobilization of the cytolytic granule components, CD107a and CD107b, also known as lysosome-associated membrane proteins LAMP-1 and LAMP-2, occurs when CD8 T cells mediate their cytolytic function and degranulate.(2) CD8 T-cell activation occurs either through the T-cell receptor (TCR)-peptide-major histocompatibility complex (MHC) or by use of a mitogen (eg, phorbol myristate acetate and the calcium ionophore ionomycin). Mitogen-mediated activation is antigen nonspecific. Impairment of global CD8 T-cell activation (due to inherent cellular immunodeficiency or as a consequence of overimmunosuppression by therapeutic agents) results in reduced production of IFN-gamma and other cytokines, reduced cytotoxic function, and increased risk for developing infectious complications. Agents associated with overimmunosuppression include the calcineurin inhibitors (eg, cyclosporine A, FK506 [Prograf/tacrolimus], and rapamycin [sirolimus]), antimetabolites (eg, mycophenolate mofetil), and thymoglobulin. Immunosuppression is most commonly used for allograft maintenance in solid organ transplant recipients, to prevent graft-versus-host disease (GVHD) in allogeneic hematopoietic stem cell transplant patients and to treat patients with autoimmune diseases. In these settings, reducing the risk for developing infectious complications as a result of overimmunosuppression is a clinical challenge. Therapeutic drug monitoring (TDM) is routinely used in the transplant practice to avoid overtreatment and to determine patient compliance. But, the levels of drugs measured in blood do not directly correlate with the administered dose due to individual pharmacokinetic differences.(3) Furthermore, drug levels may not necessarily correlate with biological activity of the drug. Consequently, it may be beneficial to consider modification of the immunosuppression regimen based on the patient's level of functional immune competence. This assay provides a means to evaluate overimmunosuppression within the CD8 T-cell compartment (global CD8 T-cell function). Intracellular IFN-gamma expression is a marker for CD8 T-cell activation. Surface CD107a and CD107b are markers for cytotoxic function. This test may be most useful when ordered at the end of induction immunosuppression and 2 to 3 months after maintenance immunosuppression to ensure that global CD8 T-cell function is not compromised. The test may also provide value when immunosuppression is increased to halt or prevent graft rejection, to provide information on a balance between overimmunosuppression with subsequent infectious comorbidities and underimmunosuppression with resultant graft rejection. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon with no change between noon and afternoon. Natural Killer (NK) cell counts, on the other hand, are constant throughout the day.(4) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(5,6,7) In fact, cortisol and catecholamine concentrations control distribution and
therefore, numbers of naive versus effector CD4 and CD8 T cells. It is generally accepted that lower CD4 T cell counts are seen in the morning compared to the evening and during summer compared to winter. These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

**Useful For:** Determining overimmunosuppression within the CD8 T-cell compartment, when used on transplant recipients and patients with autoimmune disorders receiving therapy with immunosuppressant agents

**Interpretation:** Interferon-gamma (IFN-gamma) and CD107a and CD107b expression below the defined reference range are consistent with a global impairment in CD8 T-cell function, most likely due to overimmunosuppression. IFN-gamma and CD107a and CD107b levels greater than the defined reference range are unlikely to have any clinical significance.

**Reference Values:**
Interferon-gamma (IFN-gamma) expression (as % CD8 T cells): 10.3-56.0%

CD107a/b expression (as % CD8 T cells): 8.5-49.1%

Reference values have not been established for patients who are <19 years of age.

**Clinical References:**

**CD99 (MIC-2) Immunostain, Technical Component Only**

**Clinical Information:** CD99 is the product of the MIC2 gene. It is expressed in normal tissues including some lymphocytes, pancreatic islet cells, granulosa cells of the ovary, Sertoli cells of the testis, and ependymal cells of the central nervous system. It is strongly expressed in Ewing sarcoma/primitive neuroectodermal tumor, distinguishing it from other small round blue cell tumors of childhood and adolescence.

**Useful For:** Aids in the identification of Ewing sarcoma and primitive neuroectodermal tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in...
the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**CDH1Z**

**CDH1 Gene, Full Gene Analysis**

**Clinical Information:** Hereditary diffuse gastric cancer (HDGC) is a rare autosomal dominant hereditary cancer syndrome associated with germline mutations in the CDH1 gene that encodes the protein E-cadherin. HDGC is predominantly characterized by increased susceptibility to diffuse gastric cancer and lobular breast cancer. HDGC is highly penetrant since the risk for developing gastric cancer is 80% by age 80. Women also have an approximately 40% to 60% risk of breast cancer by age 80. Colorectal cancer has been reported in individuals with germline CDH1 mutations however the specific lifetime risk for colorectal cancer is unknown. The International Gastric Cancer Linkage Consortium proposes clinical criteria for the selection of individuals who are at increased risk of having a germline CDH1 mutation as follows: 1) two or more cases of diffuse gastric cancer (histopathological confirmation in at least 1 case) in first- or second-degree relatives in which at least 1 individual is diagnosed prior to age 50; 2) three or more documented cases of diffuse gastric cancer in first- or second-degree relatives regardless of age of onset; 3) individuals diagnosed with diffuse gastric cancer before the age of 40 regardless of family history; 4) personal or family history of diffuse gastric cancer and lobular breast cancer in first and second relatives with at least 1 diagnosis occurring before age 50.

**Useful For:** Confirmation of suspected clinical diagnosis of hereditary diffuse gastric cancer Identification of familial CDH1 mutation to allow for predictive testing in family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.


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**CDKN1C Gene, Full Gene Analysis**

**Clinical Information:** Beckwith-Wiedemann syndrome (BWS) is a disorder characterized by prenatal and/or postnatal overgrowth, neonatal hypoglycemia, congenital malformations, and an increased risk for embryonal tumors. Physical findings are variable and can include abdominal wall defects, macroglossia, and hemihyperplasia. The predisposition for tumor development is associated with specific tumor types such as adrenal carcinoma, nephroblastoma (Wilms tumor), hepatoblastoma, and rhabdomyosarcoma. In infancy, BWS has a mortality rate of approximately 20%. Current data suggest that the etiology of BWS is due to dysregulation of imprinted genes in the 11p15 region of chromosome 11. Imprinting describes a difference in gene expression based on parent of origin. The majority of autosomal genes exhibit biallelic (maternal and paternal) expression, whereas imprinted genes normally express only 1 gene copy (either from the maternal or paternal allele). Imprinted genes...
are usually regulated by methylation, which prevents the gene from being expressed. Loss of expression or biallelic expression of an imprinted gene can lead to disease because of dosage imbalance. Some of the imprinted genes located in the region of 11p15 include H19 (maternally expressed), LIT1 (official symbol KCNQ1OT1; paternally expressed), IGF2 (paternally expressed), and CDKN1C (aliases p57 and KIP2; maternally expressed). Approximately 85% of BWS cases appear to be sporadic, while 15% of cases are associated with an autosomal dominant inheritance pattern. When a family history is present, the etiology is due to inherited point mutations in CDKN1C in approximately 40% of cases. The etiology of sporadic cases includes:
- Hypomethylation of LIT1: approximately 50% to 60%
- Paternal uniparental disomy of chromosome 11: approximately 10% to 20%
- Hypermethylation of H19: approximately 2% to 7%
- Unknown: approximately 10% to 20%
- Point mutation in CDKN1C: approximately 5% to 10%
- Cytogenetic abnormality: approximately 1% to 2%
- Differentially methylated region 1 (DMR1) or DMR2 microdeletion: rare

The CDKN1C gene encodes a cyclin-dependent kinase inhibitor that acts as a negative regulator of cell proliferation and fetal growth. CDKN1C also functions as a tumor suppressor gene. Normally, CDKN1C is imprinted on the paternal allele and expressed only on the maternal allele. Absence of CDKN1C expression resulting from mutations of the maternally-inherited allele is postulated to contribute to the clinical phenotype of BWS.

The appropriate first-tier test in the evaluation of a possible diagnosis of BWS is BWRS / Beckwith-Wiedemann Syndrome (BWS)/Russell-Silver Syndrome (RSS) Molecular Analysis. CDKZ / CDKN1C Gene, Full Gene Analysis should be ordered when results of BWS Methylation Analysis are negative and there is still a strong clinical suspicion of BWS. Mutations in the CDKN1C gene have also been linked to IMAGe syndrome (intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita and genital anomalies). The CDKN1C mutations associated with IMAGe syndrome tend to be missense mutations occurring in the PCNA-binding domain of the gene.

**Useful For:** Confirming a clinical diagnosis of Beckwith-Wiedemann syndrome Confirming a clinical diagnosis of intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita and genital anomalies (IMAGe) syndrome

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

### CEBPA Mutations, Gene Sequencing

**Clinical Information:** Acute myeloid leukemia (AML) with mutated CCAAT/enhancer-binding protein alpha (CEBPA) gene is a diagnostic category in the current WHO classification of hematopoietic neoplasms.(1) In addition, CEBPA mutation on both alleles (so-called double mutation status) is considered a good prognostic feature in adults with newly diagnosed AML who have a normal karyotype or do not contain an alternate diagnostic genetic abnormality.(2,3) Thus, evaluation for CEBPA mutations is necessary for accurate diagnosis in the current classification system and contributes prognostic information for a large group of AML patients.

**Useful For:** Initial evaluation of acute myeloid leukemia, both for assigning an appropriate diagnostic subclassification and as an aid for determining prognosis

**Interpretation:** The results will be given as positive or negative for CEBPA mutation and, if positive, the mutation will be described and single or double mutation status will be indicated.

**Reference Values:**
An interpretive report will be provided

**Clinical References:**

### Cedar Red (Juniperus virginiana) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal/Borderline 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 High Positive 4 5 6 17.50-49.99 50.0-99.99 >99.99 Very High Positive

**Reference Values:**
<0.35 kU/L
Cedar, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<td>Negative</td>
</tr>
<tr>
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<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


Celery IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as
Celery, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
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<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


Celiac Associated HLA-DQ Alpha 1 and DQ Beta 1 DNA Typing, Blood

Clinical Information: Celiac disease (gluten-sensitive enteropathy) is mediated by T lymphocytes in patients with genetic susceptibility. This genetic association is with certain HLA genes in the class II region (DQ alpha 1, DQ beta 1). For your convenience, we recommend utilizing cascade testing for celiac disease. Cascade testing ensures that testing proceeds in an algorithmic fashion. The following cascades are available; select the appropriate 1 for your specific patient situation. Algorithms for the cascade tests are available in Special Instructions. -CDCOM / Celiac Disease Comprehensive Cascade:
Complete testing including HLA DQ typing and serology -CDSP / Celiac Disease Serology Cascade: complete testing excluding HLA DQ -CDGF / Celiac Disease Gluten-Free Cascade: for patients already adhering to a gluten-free diet To order individual tests, see Celiac Disease Diagnostic Testing Algorithm in Special Instructions.

**Useful For:** Assessing risk of celiac disease

**Interpretation:** Most (90%-95%) patients with celiac disease have 1 or 2 copies of HLA-DQ2 haplotype (see below), while the remainder have HLA-DQ8 haplotype. Rare exceptions to these associations have been occasionally seen. In 1 study of celiac disease, only 0.7% of patients with celiac disease lacked the HLA alleles mentioned above. Results are reported as permissive, nonpermissive, or equivocal gene pairs. It is important to realize that these genes are also present in about 20% of people without celiac disease. Therefore, the mere presence of these genes does not prove the presence of celiac disease or that genetic susceptibility to celiac disease is present. The HLA-DQ molecule is composed of two chains: DQ alpha (encoded by HLA-DQA1 gene) and DQ beta (encoded by HLA-DQB1 gene).

HLA-DQ typing can be performed by serological or molecular methods. Currently most laboratories perform typing by molecular methods. HLA-DQ2 and DQ8 as typed by serology are usually based on the molecular typing of the DQB1 chain only. The current molecular method allows typing for both the DQB1 and DQA1 chains and this has shown that there are different haplotypes of HLA-DQ2 and DQ8. Typing of these haplotypes is important in celiac disease as they carry different risk association. There are 2 common haplotypes of DQ2: 1. DQA1*05:01 with DQB1*02:01 also called DQ2.5 in celiac literature 2. DQA1*02:01 with DQB1*02:02 also called DQ2.2 in celiac literature A single haplotype (heterozygote) of DQ2.5 is permissive for presence of celiac genes. However, only a double haplotype (homozygous) of DQ2.2 is permissive for presence of celiac genes. There are few reports where a single haplotype of DQ2.2 is considered to be an equivocal risk. In some cases the DQ2.2 haplotype maybe present with a DQ7.5 haplotype (DQA1*05:05 with DQB1*03:01). In this case a DQ2.5 molecule can be formed by the combination of DQB1*02:02 from 1 chromosome and DQA1*05:05 from the other chromosome. These cases fall in the same category as the DQ2.5 heterozygote. There are 3 common haplotypes of DQ8: 1. DQA1*03:01 with DQB1*03:02 2. DQA1*03:02 with DQB1*03:02 3. DQA1*03:03 with DQB1*03:02 Any single haplotype (heterozygote) of DQ8 is permissive for celiac. Therefore, the gene pairs permissive for celiac are: 1. Heterozygote (single copy) -DQA1*05:XX with DQB1*02:02 -DQA1*05:XX with DQB1*02:02 -DQA1*03:XX with DQB1*03:02 2. Heterozygous (2 copies) -DQA1*02:01 with DQB1*02:02 Gene pairs equivocal for celiac are 1. Heterozygote (single copy) -DQA1*02:01 with DQB1*02:02 2. Rare alleles of types of DQ2 and DQ8 other than those listed above All other gene pair combinations are considered non-permissive for celiac.

**Reference Values:**
An interpretive report will be provided.

than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers compared to approximately 40% of the general population. (3) A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy. (1-3) Given the invasive nature and cost of the biopsy, serologic and genetic laboratory tests may be used to identify individuals with a high probability of having celiac disease. Subsequently, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures (see Celiac Disease Comprehensive Cascade testing algorithm in Special Instructions). An individual suspected of having celiac disease may be HLA typed to determine if the individual has the susceptibility alleles DQ2 and/or DQ8. (4) In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies. (4) Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. (2) The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. The treatment for celiac disease is maintenance of a gluten-free diet. (1-3) In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves (see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions). This is typically accompanied by an improvement in clinical symptoms. For your convenience, we recommend utilizing cascade testing for celiac disease. Cascade testing ensures that testing proceeds in an algorithmic fashion. The following cascades are available; select the appropriate 1 for your specific patient situation. Algorithms for the cascade tests are available in Special Instructions. -CDCOM / Celiac Disease Comprehensive Cascade: complete testing including HLA DQ typing and serology -CDSP / Celiac Disease Serology Cascade: complete serology testing excluding HLA DQ -CDGF / Celiac Disease Gluten-Free Cascade: for patients already adhering to a gluten-free diet. To order individual tests, see Celiac Disease Diagnostic Testing Algorithm in Special Instructions. It should be noted that HLA typing is not required to establish a diagnosis of celiac disease. Consider ordering CDSP / Celiac Disease Serology Cascade if HLA typing is not desired or has been previously performed.

**Useful For:** Evaluating patients suspected of having celiac disease, including patients with compatible symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disease) Comprehensive algorithmic evaluation including HLA typing

**Interpretation:** Immunoglobulin A (IgA): Total IgA levels below the age-specific reference range suggest either a selective IgA deficiency or a more generalized immunodeficiency. For individuals with a low IgA level, additional clinical and laboratory evaluation is recommended. Some individuals may have a partial IgA deficiency in which the IgA levels are detectable but fall below the age-adjusted reference range. For these individuals both IgA and IgG isotypes for tTG and deamidated gliadin antibodies are recommended for the evaluation of celiac disease; IgA-tTG, IgG-tTG, IgA-deamidated gliadin, and IgG-deamidated gliadin antibody assays are performed in this cascade. For individuals who have selective IgA deficiency with undetectable levels of IgA, only IgG-tTG and IgG-deamidated gliadin antibody assays are performed. HLA-DQ Typing: Approximately 90% to 95% of patients with celiac disease have the HLA DQ2 allele; most of the remaining patients with celiac disease have the HLA DQ8 allele. Individuals who do not carry either of these alleles are unlikely to have celiac disease. However, individuals with these alleles may not, during their lifetime, develop celiac disease. Therefore, the presence of DQ2 or DQ8 does not conclusively establish a diagnosis of celiac disease. Individuals with DQ2 and/or DQ8 alleles, in the context of positive serology and compatible clinical symptoms, should be referred for small intestinal biopsy. HLA typing may be especially helpful for those patients who have begun to follow a gluten-free diet prior to a confirmed diagnosis of celiac disease. (4) Tissue Transglutaminase (tTG) Antibody, IgA/IgG: Individuals positive for tTG antibodies of the IgA isotype likely have celiac disease and small intestinal biopsy is recommended. For individuals with selective IgA deficiency, testing for tTG antibodies of the IgG isotype is performed. In these individuals, a positive IgG-tTG antibody result suggests a diagnosis of celiac disease. However, just as with the IgA-tTG antibody, a biopsy should be performed to confirm the diagnosis. Negative tTG IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet. Gliadin (Deamidated) Antibody, IgA/IgG: Positivity for deamidated gliadin antibodies of the IgA isotype is suggestive of celiac disease, and small intestinal biopsy is recommended. For individuals with selective IgA deficiency, testing for deamidated gliadin antibodies of the IgG isotype is performed. In these
individuals, a positive IgG-deamidated gliadin antibody result suggests a diagnosis of celiac disease. However, just as with the IgA-deamidated gliadin antibody, a biopsy should be performed to confirm the diagnosis. Negative deamidated gliadin IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet. Endomysial (EMA) Antibody, IgA: Positivity for EMA antibodies of the IgA isotype is suggestive of celiac disease, and small intestinal biopsy is recommended. For individuals with selective IgA deficiency, evaluation of EMA antibodies is not indicated. Negative EMA antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet.

**Reference Values:**

**IMMUNOGLOBULIN A (IgA)**

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<th>Reference Range (mg/dL)</th>
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</tr>
<tr>
<td>5-&lt;9 months</td>
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<tr>
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<td>60-337 mg/dL</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td>61-356 mg/dL</td>
</tr>
</tbody>
</table>

**HLA-DQ TYPING**

Presence of DQ2 or DQ8 alleles associated with celiac disease


**Celiac Disease Gluten-Free Cascade**

**Useful For:** Evaluating patients suspected of having celiac disease who are currently (or were recently) on a gluten-free diet

**Interpretation:** HLA-DQ Typing: Approximately 90% to 95% of patients with celiac disease have the HLA-DQ2 allele; most of the remaining patients with celiac disease have the HLA-DQ8 allele. Individuals who do not carry either of these alleles are unlikely to have celiac disease. For these individuals, no further serologic testing is required. However, individuals with these alleles may not, during their lifetime, develop celiac disease. Therefore, the presence of DQ2 or DQ8 does not conclusively establish a diagnosis of celiac disease. For individuals with DQ2 and/or DQ8 alleles, in the context of positive serology and compatible clinical symptoms, small intestinal biopsy is recommended. Immunoglobulin A (IgA): Total IgA levels below the age-specific reference range suggest either a selective IgA deficiency or a more generalized immunodeficiency. For individuals with a low IgA level, additional clinical and laboratory evaluation is recommended. Some individuals may have a partial IgA deficiency in which the IgA levels are detectable, but fall below the age-adjusted reference range. For these individuals, both IgA and IgG isotypes for tTG and deamidated gliadin antibodies are recommended for the evaluation of celiac disease. Tissue Transglutaminase (tTG) Antibody, IgA/IgG: Individuals positive for tTG antibodies of the IgA and/or IgG isotype may have celiac disease and small intestinal biopsy is recommended. Negative tTG IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet. Gliadin (Deamidated) Antibody, IgA/IgG: Positivity for deamidated gliadin antibodies of the IgA and/or IgG isotype is suggestive of celiac disease, and small intestinal biopsy is recommended. Negative deamidated gliadin IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet.
Celiac Disease Serology Cascade

Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process following ingestion of wheat, rye, or barley proteins that occurs in genetically susceptible individuals.(1) The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy.(1) Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and constipation.(2) Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis.(3) Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma.(1,2) The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency.(1,3) Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared with approximately 40% of the general population.(3) A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy.(1-3) Given the invasive nature and cost of the biopsy, serologic and genetic laboratory tests may be used to identify individuals with a high probability of having celiac disease. Subsequently, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures. In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies.(4) Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient.(2) The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. The treatment for celiac disease is maintenance of a gluten-free diet.(1-3) In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves (see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions). This is typically accompanied by an improvement in clinical symptoms For your convenience, we recommend utilizing cascade testing for celiac disease. Cascade testing ensures that testing proceeds in an algorithmic fashion. The following cascades are available; select the appropriate one for your specific patient situation. Algorithms for the cascade tests are available in Special Instructions. -CDCOM / Celiac Disease Comprehensive Cascade: complete testing including HLA DQ typing and serology -CDSP / Celiac Disease Serology Cascade: complete serology testing excluding HLA DQ -CDGF / Celiac Disease Gluten-Free Cascade: for patients already adhering to a gluten-free diet To order individual tests, see Celiac Disease Diagnostic Testing Algorithm in Special Instructions.

Useful For: Evaluating patients suspected of having celiac disease, including patients with compatible symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disease, positivity for DQ2 and/or DQ8)

Interpretation: Immunoglobulin A (IgA): Total IgA levels below the age-specific reference range suggest either a selective IgA deficiency or a more generalized immunodeficiency. For individuals with a low IgA level, additional clinical and laboratory evaluation is recommended. Some individuals may have a partial IgA deficiency in which the IgA levels are detectable but fall below the age-adjusted reference range. For these individuals, both IgA and IgG isotypes for tTG and deamidated gliadin antibodies are recommended for the evaluation of celiac disease; IgA-tTG, IgG-tTG, IgA-deamidated gliadin, and IgG-deamidated gliadin antibody assays are performed in this cascade. For individuals who have selective IgA deficiency or undetectable levels of IgA, only IgG-tTG and IgG-deamidated gliadin antibody assays are performed. Tissue Transglutaminase (tTG) Ab, IgA/IgG: Individuals positive for
TG antibodies of the IgA isotype likely have celiac disease and a small intestinal biopsy is recommended. For individuals with selective IgA deficiency, testing for tTG antibodies of the IgG isotype is performed. In these individuals, a positive IgG-tTG antibody result suggests a diagnosis of celiac disease. However, just as with the IgA-tTG antibody, a biopsy should be performed to confirm the diagnosis. Negative tTG IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet. Gliadin (Deamidated) Ab, IgA/IgG: Positivity for deamidated gliadin antibodies of the IgA isotype is suggestive of celiac disease; small intestinal biopsy is recommended. For individuals with selective IgA deficiency, testing for deamidated gliadin antibodies of the IgG isotype is performed. In these individuals, a positive IgG-deamidated gliadin antibody result suggests a diagnosis of celiac disease. However, just as with the IgA-deamidated gliadin antibody, a biopsy should be performed to confirm the diagnosis. Negative deamidated gliadin IgA and/or IgG antibody serology does not exclude a diagnosis of celiac disease, as antibody levels decrease over time in patients who have been following a gluten-free diet. Endomysial (EMA) Ab, IgA: Positivity for EMA antibodies of the IgA isotype is suggestive of celiac disease, and small intestinal biopsy is recommended. For individuals with selective IgA deficiency, evaluation of EMA antibodies is not indicated. Negative EMA antibody serology does not exclude a diagnosis of celiac disease as antibody levels decrease over time in patients who have been following a gluten-free diet.

Reference Values:
Immunoglobulin A
0-<5 months: 7-37 mg/dL
5-<9 months: 16-50 mg/dL
9-<15 months: 27-66 mg/dL
15-<24 months: 36-79 mg/dL
2-<4 years: 27-246 mg/dL
4-<7 years: 29-256 mg/dL
7-<10 years: 34-274 mg/dL
10-<13 years: 42-295 mg/dL
13-<16 years: 52-319 mg/dL
16-<18 years: 60-295 mg/dL
> or =18 years: 61-356 mg/dL

Clinical References:
4. Update on celiac disease: New standards and new tests. 2008 Mayo Communique

Cell Count and Differential, Body Fluid
Clinical Information: Body fluids, other than the commonly analyzed urine and blood, include synovial, pleural, peritoneal, and pericardial fluids. These fluids may be present in increased volumes and/or may contain increased numbers of normal and/or abnormal cells in a variety of disease states.

Useful For: Aids in the diagnosis of joint disease, systemic disease, inflammation, malignancy, infection, and trauma

Interpretation: Trauma and hemorrhage may result in increased red and white cells; red cells predominate. White blood cells are increased in inflammatory and infectious processes: -Neutrophils predominate in bacterial infections -Lymphocytes predominate in viral infections -Macrophages may be increased in inflammatory and infectious processes -Eosinophils may be increased in parasitic or fungal infections

Reference Values:
TOTAL NUCLEATED CELLS
Synovial fluid: <150/mcL
Peritoneal/pleural/pericardial fluid: <500/mcL
NEUTROPHILS
Synovial Fluid: <25%
Peritoneal/pleural/pericardial fluid: <25%
LYMPHOCYTES
Synovial fluid: <75%
MONOCYTES/MACROPHAGES
Synovial fluid: <=70%


Cell-Bound Platelet Autoantibody Screen, Blood

Clinical Information: Platelet antibodies may be allo- or autoantibodies and may be directed to a wide range of antigenic "targets" carried on platelet cytoplasmic membranes. Cell-bound platelet antibody test (direct) is optimized to identify the presence of antibodies bound to the patient's platelet surface. Platelet autoantibodies are involved in several clinical situations such as: -Idiopathic (autoimmune) thrombocytopenic purpura (ITP) -Thrombocytopenia associated with systemic lupus erythematosus -Thrombocytopenia associated with sepsis (usually bacterial, occasionally fungal) In most studies of autoimmune thrombocytopenia, the majority (approximately 80%) of detected autoantibodies were directed to the platelet glycoprotein IIb/IIIa and, more rarely, to other glycoproteins such as Ib/IX (approximately 11%) or Ia/IIa. This test is not recommended for the detection of alloimmune thrombocytopenic conditions like immune refractoriness to platelets, posttransfusion purpura, or alloimmune neonatal thrombocytopenia; PLABN / Platelet Antibody Screen, Serum is recommended for these conditions.

Useful For: Diagnosis of idiopathic (autoimmune) thrombocytopenic purpura (ITP) and diagnosis of immune thrombocytopenia associated with systemic lupus erythematosus or other disorders associated with autoimmune phenomena

Interpretation: A test result showing optical density (OD) values equal to or greater than the cutoff of the negative controls (run specific) corresponding to the glycoprotein is regarded as positive results. The patient report will include an overall interpretation and a negative/positive result for each glycoprotein (GPIIb/IIIa, GPIb/IX, and GPIa/IIa). Additionally, the patients observed OD value and the negative control cutoff value for the patient-specific assay run will be included on the report. A positive test in the presence of thrombocytopenia (not explained by other findings) is suggestive of idiopathic (autoimmune) thrombocytopenic purpura. Similarly, a positive test in a thrombocytopenic patient with systemic lupus erythematosus is consistent with an autoimmune cause. Patients who are septic may also have a positive test with reactivity against most glycoproteins. Presence of reactivity to some glycoproteins has no clearly established clinical significance. Borderline positive results need to be interpreted in the right clinical context.

Reference Values:
Not applicable

**Cell-Free DNA BRAF V600 Test, Blood**

**Clinical Information:** This test uses DNA extracted from the peripheral blood to evaluate for the presence of BRAF V600E and V600K mutations. A positive result indicates the presence of an activating BRAF mutation and may be useful for guiding the treatment of individuals with melanoma. Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the FDA for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks.

**Useful For:** An alternative to invasive tissue biopsies for the determination of BRAF V600E and V600K mutations Identification of patients with melanoma who are most likely to benefit from targeted therapies

**Interpretation:** An interpretive report will be provided.


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**Cell-Free DNA EGFR Exon 18, 19, 20, 21, Mutation Analysis, Blood**

**Clinical Information:** Approximately 25% of non-small cell lung cancers (NSCLC) have mutations in the EGFR gene. Most mutations occur in hotspot regions in exons 18, 19, 20 and 21. EGFR is activated by the binding of specific ligands, resulting in activation of the RAS/mitogen-activated protein kinase (MAPK) pathway. EGFR-targeted therapies (eg, gefitinib and erlotinib) have been approved by the FDA for use in treating patients with NSCLC who previously failed to respond to traditional chemotherapy. Current data suggest that the efficacy of EGFR-targeted therapies in NSCLC is confined to patients with tumors demonstrating the presence of EGFR-activating mutations such as L858R, L861Q, G719A/S/C, S768I, or small deletions within exon 19 and the absence of drug-resistant mutations (eg, exon 20 insertions and T790M). As a result, the mutation status of EGFR is a critical marker for selecting patients for EGFR-targeted therapy. This FDA approved test uses DNA extracted from the peripheral blood to evaluate for the presence of mutations in exons 18, 19, 20, and 21 of the EGFR gene. A positive result indicates the presence of an EGFR mutation and may be useful for guiding the treatment of individuals with non-small cell lung cancer. At this time, this test is approved specifically for patients with lung cancer. The utilization of this test in patients with other tumor types could be considered an off-label use of this test.

**Useful For:** As an alternative to invasive tissue biopsies for the determination of EGFR-mutation status Selection of patients with non-small cell lung cancer who are most likely to benefit from targeted therapies

**Interpretation:** An interpretive report will be provided.


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**Cell-Free DNA EGFR T790M Mutation Analysis, Blood**

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 494
**Clinical Information:** EGFR-targeted tyrosine kinase inhibitors (eg, gefitinib and erlotinib) have been approved by the FDA for use in treating patients with non-small cell lung cancer (NSCLC) who previously failed to respond to traditional chemotherapy. However, the EGFR T790M mutation is associated with acquired resistance to tyrosine kinase inhibitor (TKI) therapy in about 60% of patients with disease progression after initial response to erlotinib, gefitinib, or afatinib. Recent data suggest that patients with metastatic NSCLC and the T790M mutation may benefit from osimertinib, an FDA-approved oral TKI that inhibits both EGFR-activating mutations and the T790M mutation.

**Useful For:** Determination of EGFR T790M mutation status in blood specimens as an alternative to invasive tissue biopsies Identification of patients with non-small cell lung cancer who harbor a T790M mutation and may benefit from specific EGFR-targeted therapies

**Interpretation:** An interpretive report will be provided.

**Clinical References:**

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**Cell-free DNA KRAS 12, 13, 61,146, Blood**

**Clinical Information:** Approximately 30% to 50% of colorectal cancers (CRC) have mutations in KRAS. Most occur in hotspot regions in codons 12, 13, 61, and 146. These mutations lead to constitutive activation of the RAS/MAPK pathway downstream of epidermal growth factor receptor (EGFR), limiting the effectiveness of anti-EGFR therapies, such as cetuximab and panitumumab, which inhibit ligand-mediated activation of EGFR. Therefore, identification and quantitation of these mutations is critical in selecting the appropriate therapy. This test uses DNA extracted from peripheral blood to evaluate for the presence of KRAS (G12A, G12C, G12D, G12R, G12S, G12V, G13D, Q61K, Q61L, Q61R, Q61H, and A146T) mutations. A positive result indicates the presence of an activating KRAS mutation and may be useful for guiding the treatment of individuals with colorectal cancer.

**Useful For:** As an alternative to invasive tissue biopsies for the determination of KRAS 12, 13, 61,146 (G12A, G12C, G12D, G12R, G12S, G12V, G13D, Q61K, Q61L, Q61R, Q61H, and A146T) mutation status Selection of patients with colorectal cancer who are most likely to benefit from epidermal growth factor receptor (EGFR)-targeted therapies

**Interpretation:** An interpretive report will be provided.

**Clinical References:**

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**Cell-Free DNA Prenatal Screen**

**Clinical Information:** This test provides the ability to detect common chromosome abnormalities, specifically aneuploidy including Down syndrome (trisomy 21), Patau syndrome (trisomy 13), and Edward syndrome (trisomy 18), without the risk of pregnancy loss associated with invasive prenatal procedures. Chromosomal aneuploidy is the leading known genetic cause of miscarriage and congenital birth defects. This fetal DNA screen is not a diagnostic test; therefore, abnormal results should be confirmed with invasive prenatal diagnostic testing (such as chorionic villi sampling or amniocentesis) and a genetic consultation is recommended. In addition, a negative result does not ensure an unaffected...
The false-negative rate for trisomy 21 is less than 1%, for trisomy 18 is 3.6%, and for trisomy 13 is 9.4%. The positive predictive value in low-risk pregnancies is lower than in pregnancies at high risk for aneuploidy.

**Useful For:** Noninvasive screening for aneuploidies of chromosomes 13, 18, and 21 in pregnancies

**Interpretation:** Normal representation of material from chromosomes 13, 18, and 21 will be reported as normal, indicating a low risk for trisomy 13, trisomy 18, and trisomy 21 in the fetus. Fetal sex will be reported. If Y chromosome material is detected, this is suggestive of a male fetus. If Y chromosome material is not detected, this is suggestive of a female fetus. Increased amounts of chromosomal material will be reported as positive for having a trisomy of the identified chromosome for chromosomes 13, 18, or 21. While most specimens undergoing this analysis can be readily characterized, on rare occasions equivocal or incidental results such as aneuploidy of chromosomes other than 13, 18, and 21 as well as other genomic unbalanced rearrangements, may not allow for standard interpretation of this aneuploidy screen. In these situations, a new maternal blood specimen may be requested or a recommendation for other screening measures or diagnostic cytogenetic testing will be made.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
2. ACOG/SMFM Joint Committee Opinion: Noninvasive prenatal testing for fetal aneuploidy. No. 640, Dec 2015

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**Cell-Free DNA Prenatal Screen, Autosomal Trisomy and Sex Chromosome Aneuploidy**

**Clinical Information:** This test provides the ability to detect common chromosome abnormalities, specifically aneuploidy including Down syndrome (trisomy 21), Patau syndrome (trisomy 13), Edward syndrome (trisomy 18), monosomy X, 47,XXX, 47,XYY, and Klinefelter syndrome (XXY), without the risk of pregnancy loss associated with invasive prenatal procedures. Chromosomal aneuploidy is the leading known genetic cause of miscarriage and congenital birth defects. This fetal DNA screen is not a diagnostic test; therefore, abnormal results should be confirmed with invasive prenatal diagnostic testing (such as chorionic villi sampling or amniocentesis) and a genetic consultation is recommended. In addition, a negative result does not ensure an unaffected pregnancy. The false-negative rate for trisomy 21 is less than 1%, for trisomy 18 is 3.6%, for trisomy 13 is 9.4%, for monosomy X is 9.0%, and for sex chromosome aneuploidies other than monosomy X it is 3.6%. The positive predictive value in low-risk pregnancies is lower than in pregnancies at high risk for aneuploidy.

**Useful For:** Noninvasive screening for aneuploidies of chromosomes 13, 18, 21, and sex chromosomes X and Y in pregnancies

**Interpretation:** Normal representation of material from chromosomes 13, 18, 21, X, and Y will be reported as normal, indicating a low risk for trisomy 13, trisomy 18, trisomy 21, and sex chromosome aneuploidies in the fetus. Fetal sex will be reported. If Y chromosome material is detected, this is suggestive of a male fetus. If Y chromosome material is not detected, this is suggestive of a female fetus. Increased amounts of autosomal chromosomal material will be reported as positive for having a trisomy of chromosome 13, 18, or 21. This screen will also report abnormal amounts of chromosomal material of...
sex chromosomes X and Y, including monosomy X, XXX, XXY, and XYY. While most specimens undergoing this analysis can be readily characterized, on rare occasions equivocal or incidental results such as aneuploidy of chromosomes other than 13, 18, 21, X, Y, as well as other genomic unbalanced rearrangements, may not allow for standard interpretation of this aneuploidy screen. In these situations, a new maternal blood specimen may be requested or a recommendation for other screening measures or diagnostic cytogenetic testing will be made.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Central Nervous System Consultation, Autopsy**

**Clinical Information:** Difficult neurological abnormalities, including congenital anomalies, sometimes require the assistance of a neuropathologist. This evaluation is offered to provide the careful dissection and diagnostic experience that may be needed for unusual or rare neuropathological cases.

**Useful For:**
- Evaluation of congenital neurological disease
- Evaluation of neurodegenerative disease
- Evaluation of cases with a complex neurological or neurosurgical history
- Evaluation of sudden unexplained death
- Not for cases under litigation without preauthorization

**Interpretation:** This request will be processed as a consultation. Appropriate stains will be performed and a diagnostic interpretation provided.

**Reference Values:**
This request will be processed as a consultation. Appropriate dissection will be performed and an interpretive report provided.

**Clinical References:**

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**Centromere Antibodies, IgG, Serum**

**Clinical Information:** Centromere antibodies occur primarily in patients with the calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia (CREST) syndrome variant of systemic sclerosis (scleroderma). CREST syndrome is characterized by the following clinical features: calcinosis, Raynaud phenomenon, esophageal hypomotility, sclerodactyly, and telangiectasia. (1) Centromere antibodies were originally detected by their distinctive pattern of fine-speckled nuclear staining on cell substrates used in the fluorescent antinuclear antibody test. (2) In subsequent studies, centromere antibodies were found to react with several centromere proteins of 18
kDa, 80 kDa, and 140 kDa named as CENP-A, CENP-B, and CENP-C, respectively. Several putative epitopes associated with these autoantigens have been described. The CENP-B antigen is believed to be the primary autoantigen and is recognized by all sera that contain centromere antibodies.

**Useful For:** Evaluating patients with clinical signs and symptoms compatible with systemic sclerosis including skin involvement, Raynaud phenomenon, and arthralgias. Aiding in the diagnosis of calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasis (CREST) syndrome.

**Interpretation:** In various reported clinical studies, centromere antibodies occur in 50% to 96% of patients with calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasis (CREST) syndrome. A positive test for centromere antibodies is strongly associated with CREST syndrome. The presence of detectable levels of centromere antibodies may antedate the appearance of diagnostic clinical features of CREST syndrome by several years.

**Reference Values:**

- <1.0 U (negative)
- ≥1.0 U (positive)

Reference values apply to all ages.

**Clinical References:**


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**Cephalosporium acremonium, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1 0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2 0.70-3.49</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Ceramide Trihexosides and Sulfatides, Urine

Clinical Information: Urinary excretion of ceramide trihexosides can be suggestive of Fabry disease, while excretion of sulfatide with or without ceramide trihexosides can be suggestive of metachromatic leukodystrophy, multiple sulfatase deficiency, mucolipidosis II (I-cell disease), or saposin B deficiency. Fabry disease is an X-linked recessive lysosomal storage disorder caused by a deficiency of the enzyme alpha-galactosidase A (alpha-Gal A). Reduced enzyme activity results in accumulation of glycosphingolipids in the lysosomes throughout the body, in particular, the kidney, heart, and brain. Severity and onset of symptoms are dependent on the residual enzyme activity. Symptoms may include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, corneal opacity, renal insufficiency leading to end-stage renal disease, and cardiac and cerebrovascular disease. There are renal and cardiac variant forms of Fabry disease that may be underdiagnosed. Females who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected, and they may have alpha-Gal A activity in the normal range. Individuals with Fabry disease, regardless of the severity of symptoms, may show an increased excretion of ceramide trihexoside in urine. Metachromatic leukodystrophy (MLD) is an autosomal recessive lysosomal storage disorder caused by a deficiency of the arylsulfatase A enzyme, which leads to the accumulation of various sulfatides in the brain, nervous system, and visceral organs, including the kidney and gallbladder. The 3 clinical forms of MLD are late-infantile, juvenile, and adult, depending on age of onset. All result in progressive neurologic changes and leukodystrophy demonstrated on magnetic resonance imaging. Symptoms may include hypotonia, clumsiness, diminished reflexes, slurred speech, behavioral problems, and personality changes. Individuals with MLD typically show an increased excretion of sulfatides in urine. Low arylsulfatase A activity has been found in some clinically normal parents and other relatives of MLD patients. These individuals do not have metachromatic deposits in peripheral nerve tissues, and their urine content of sulfatides is normal. Individuals with this "pseudodeficiency" have been recognized with increasing frequency among patients with other apparently unrelated neurologic conditions as well as among the general population. This has been associated with a fairly common polymorphism in the arylsulfatase A gene, which leads to low expression of the enzyme (5%-20% of normal). Saposin B deficiency is a rare autosomal recessive disorder with symptoms that mimic MLD. Age of onset dictates the clinical subtypes of saposin B deficiency. Individuals with saposin B deficiency have normal arylsulfatase A activity. In urine, individuals with saposin B deficiency have an increased excretion of sulfatides and may also show increased excretion of ceramide trihexosides. Multiple sulfatase deficiency (MSD) is another rare autosomal recessive disorder that mimics the symptoms of MLD. In addition, individuals with MSD also may have clinical manifestations that resemble mucopolysaccharidoses. MSD results in deficiencies in all sulfatases including arylsulfatase A and B. Individuals with MSD have an increased excretion of sulfatides in their urine. Mucolipidosis II, also known as I-cell disease, is a rare autosomal recessive disorder with features of both mucopolysaccharidoses and sphingolipidoses. It is characterized by congenital or early infantile manifestations including coarse facial features, short stature, skeletal anomalies, cardio- and hepatomegaly, and developmental delays. This is a progressive disorder and death typically occurs in the first decade of life. Individuals with I-cell disease typically show an increased excretion of ceramide trihexosides and sulfatides in urine.

Useful For: Identifying patients with Fabry disease Identifying patients with metachromatic
leukodystrophy Identifying patients with saposin B deficiency Identifying patients with multiple sulfatase deficiency Identifying patients with mucolipidosis II (I-cell disease)

**Interpretation:** The pattern of ceramide trihexosides or sulfatide excretion will be described. A normal pattern of excretion suggests absence of disease (see Cautions). Evidence of ceramide trihexoside accumulation suggests decreased or deficient alpha-galactosidase activity. Follow-up testing with the specific enzyme assay recommended: -AGA / Alpha-Galactosidase, Leukocytes -AGABS / Alpha-Galactosidase, Blood Spot -AGAS / Alpha-Galactosidase, Serum Evidence of sulfatide accumulation suggests decreased or deficient arylsulfatase A activity. Follow-up with the specific enzyme assay recommended: -ARSAW / Arylsulfatase A, Leukocytes -ARSU / Arylsulfatase A, 24 Hour, Urine To exclude multiple sulfatase deficiency (MSD), simultaneous determination of ARSB / Arylsulfatase B, Fibroblasts and I2SW / Iduronate-2-sulfatase, Whole Blood (or I2SBS / Iduronate-2-Sulfatase, Blood Spot) is recommended. Evidence of both ceramide trihexoside and sulfatide accumulation suggests a diagnosis of mucolipidosis II (I-cell disease) or saposin B deficiency. Follow-up testing to rule-out I-cell disease may include: -NAGS / Hexosaminidase A and Total Hexosaminidase, Serum -AGAS / Alpha-Galactosidase, Serum or ANAS / Alpha-N-Acetylglucosaminidase, Serum Molecular genetic testing is required to confirm saposin B deficiency. See Fabry Disease Testing Algorithm in Special Instructions.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

**CTSNSR 37998 Ceramide Trihexosides and Sulfatides, Urine**

**Clinical Information:** This test measures urinary excretion of ceramide trihexosides and sulfatides which are elevated in patients with Fabry disease, metachromatic leukodystrophy, multiple sulfatase deficiency, mucolipidosis II (I-cell disease), or saposin B deficiency.

**Useful For:** See LYSUDU / Lysosomal Storage Disorders Screen, Urine

**Interpretation:** The pattern of ceramide trihexosides or sulfatide excretion will be described. A normal pattern of excretion suggests absence of disease (see Cautions). Evidence of ceramide trihexoside accumulation suggests decreased or deficient alpha-galactosidase activity. Follow-up testing with the specific enzyme assay recommended: -AGA / Alpha-Galactosidase, Leukocytes -AGABS / Alpha-Galactosidase, Blood Spot -AGAS / Alpha-Galactosidase, Serum Evidence of sulfatide accumulation suggests decreased or deficient arylsulfatase A activity. Follow-up with the specific enzyme assay recommended: -ARSAW / Arylsulfatase A, Leukocytes -ARSU / Arylsulfatase A, 24 Hour, Urine To exclude multiple sulfatase deficiency (MSD), simultaneous determination of ARSB / Arylsulfatase B, Fibroblasts and I2SW / Iduronate-2-sulfatase, Whole Blood (or I2SBS / Iduronate-2-Sulfatase, Blood Spot) is recommended. Evidence of both ceramide trihexoside and sulfatide accumulation suggests a diagnosis of mucolipidosis II (I-cell disease) or saposin B deficiency. Follow-up testing to rule-out I-cell disease may include: -NAGS / Hexosaminidase A and Total Hexosaminidase, Serum -AGAS / Alpha-Galactosidase, Serum or ANAS / Alpha-N-Acetylglucosaminidase, Serum Molecular genetic testing is required to confirm saposin B deficiency. See Fabry Disease Testing Algorithm in Special Instructions.
disease may include: -NAGS / Hexosaminidase A and Total Hexosaminidase, Serum -AGAS / Alpha-Galactosidase, Serum or ANAS / Alpha-N-Acetylglucosaminidase, Serum Molecular genetic testing is required to confirm saposin B deficiency.

Reference Values:
Only orderable as part of a profile. See LYSDU / Lysosomal Storage Disorders Screen, Urine.

For more information regarding ceramide trihexosides and sulfatides, see CTSA / Ceramide Trihexosides and Sulfatides, Urine.


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CERAM 65054

Ceramides, Plasma

Clinical Information: Plasma ceramides are predictors of adverse cardiovascular events resulting from unstable atherosclerotic plaque. Ceramides are complex lipids that play a central role in cell membrane integrity, cellular stress response, inflammatory signaling, and apoptosis. Synthesis of ceramides from saturated fats and sphingosine occurs in all tissues. Metabolic dysfunction and dyslipidemia results in accumulation of ceramides in tissues not suited for lipid storage. Elevated concentrations of circulating ceramides are associated with atherosclerotic plaque formation,(1) ischemic heart disease, myocardial infarction,(2,3) hypertension,(4) stroke,(5) type 2 diabetes mellitus, insulin resistance and obesity.(6) Three specific ceramides have been identified as highly linked to cardiovascular disease and insulin resistance: Cer16:0, Cer18:0, and Cer24:1. Individuals with elevated plasma ceramides are at higher risk of major adverse cardiovascular events even after adjusting for age, gender, smoking status, and serum biomarkers such as low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, c-reactive protein (CRP) and lipoprotein-associated phospholipase A2 (Lp-PLA2). Direct interventional studies have not yet been reported; however, ceramide concentrations are reduced by current cardiovascular therapies including statins, ezetimibe, and Proprotein convertase subtilisin/kexin type 9 (PCSK9) activity.(3,7)

Useful For: Evaluation for risk of major adverse events due to cardiovascular disease within the next 1 to 5 years

Interpretation: Elevated plasma ceramides are associated with increased risk of myocardial infarction, acute coronary syndromes, and mortality within 1 to 5 years. Ceramide Score Relative Risk Risk Category 0-2 1.0 Lower 3-6 1.8 Moderate 7-9 2.3 Increased 10-12 5.1 Higher Score is based on trial data including >4,000 subjects.

Reference Values:
Ceramide (16:0): 0.19-0.36 mcmol/L
Ceramide (18:0): 0.05-0.14 mcmol/L
Ceramide (24:1): 0.65-1.65 mcmol/L
Ceramide (16:0)/(24:0): <0.11
Ceramide (18:0)/(24:0): <0.05
Ceramide (24:1)/(24:0): <0.45
Ceramide Risk Score:
0-2 Lower risk
3-6 Moderate risk
7-9 Increased risk
10-12 Higher risk

Reference values have not been established for patients who are <18 years of age.

Note: Ceramide (24:0) alone has not been independently associated with disease and will not be reported.

**Clinical References:**

DOI:10.1093/eurheartj/ehw148

**Cerebrospinal Fluid (CSF) IgG Index**

**Clinical Information:** Elevation of IgG levels in the cerebrospinal fluid (CSF) of patients with inflammatory diseases of the central nervous system (multiple sclerosis [MS], neurosyphilis, acute inflammatory polyradiculoneuropathy, subacute sclerosing panencephalitis) is due to local central nervous system (CNS) synthesis of IgG. The 2 most commonly used diagnostic laboratory tests for MS are CSF index and oligoclonal banding. The CSF index is the CSF IgG to CSF albumin ratio compared to the serum IgG to serum albumin ratio. The CSF index is, therefore, an indicator of the relative amount of CSF IgG compared to serum. Any increase in the index is a reflection of IgG production in the CNS. The IgG synthesis rate is a mathematical manipulation of the CSF index data and can also be used as a marker for CNS inflammatory diseases.

**Useful For:** As an aid in the diagnosis of multiple sclerosis

**Interpretation:** Cerebrospinal fluid (CSF) IgG index is positive (elevated) in approximately 80% of patients with multiple sclerosis (MS). Oligoclonal banding in CSF is also positive in approximately 80% of patients with MS. The use of CSF index plus oligoclonal banding has been reported to increase the sensitivity to over 90%. The index is independent of the activity of the demyelinating process.

**Reference Values:**

<table>
<thead>
<tr>
<th>CSF index</th>
<th>0.00-0.85</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF IgG</td>
<td>0.0-8.1 mg/dL</td>
</tr>
<tr>
<td>CSF albumin</td>
<td>0.0-27.0 mg/dL</td>
</tr>
<tr>
<td>Serum IgG</td>
<td>0.0-33.4 mg/dL</td>
</tr>
<tr>
<td>0-4 months</td>
<td>164-588 mg/dL</td>
</tr>
<tr>
<td>5-8 months</td>
<td>246-904 mg/dL</td>
</tr>
<tr>
<td>9-12 months</td>
<td>313-1,170 mg/dL</td>
</tr>
<tr>
<td>2-3 years</td>
<td>285-1,156 mg/dL</td>
</tr>
</tbody>
</table>
Certolizumab pegol and Anti-Certolizumab Antibodies, Serum

Clinical Information:

**Interpretation:** Certolizumab (CZP) - Endoscopic response and remission are associated with higher plasma concentrations of certolizumab pegol (CZP). A significant inverse relationship has been found between plasma concentration of CZP and C-reactive protein. In a study of CZP dose optimization in patients with CD, remission rates were higher in patients whose CZP levels were greater than 27.5 ug/mL using an in-house ELISA assay. Inform Tx drug levels were validated with drug levels measured by the UCB in-house ELISA assay. The tests had good correlation, although Inform Tx tended to consistently measure 19% higher than the in-house test. The association between CZP levels and achievement of several definitions of clinical response has been studied in a large pooled dataset of pivotal trials. The CZP levels measured by InformTx have been extrapolated to be: Week 6 CZP > or = 43 ug/mL associated with CDAI < 150 and FC > or = 250 ug/mL; Week 12, CZP levels > or = 18 ug/mL associated with CDAI < 150 and FC > or = 250 ug/mL at week 26. Antibodies to Certolizumab - Clinical trials exploring CZP immunogenicity have not found a relationship between development of antibodies to certolizumab (ATC) and clinical response. Some patients on anti-TNF therapy may develop antibodies that resolve over time. The presence of antibodies to certolizumab has been associated with decreased serum CZP levels and decreased clinical efficacy in rheumatoid arthritis trials. In patients with CD that fail to respond to anti TNF therapy but have a therapeutic drug concentration and low or undetectable antibody levels, clinical guidelines suggest a switch to another drug class. In patients with Irritable Bowel Disease (IBD) with good response to other biologic therapies, supra therapeutic doses have been reduced without disease flares, resulting in significant cost savings.

**Reference Values:**
Clinically Reportable Ranges:
- Certolizumab 3-84 ug/mL
- Anti-Certolizumab antibody 10 - 160 AU/mL

**Clinical References:**
disease patients to account for time varying nature of covariates. IBD. 2016 Mar;22 (Supp 1):P103. 5.

Ceruloplasmin, Serum

Clinical Information: Ceruloplasmin is a positive acute-phase reactant and a copper-binding protein that accounts for over 95% of serum copper in normal adults. Ceruloplasmin is measured primarily to assist with a diagnosis of Wilson disease. Other indications include Menkes disease, dietary copper insufficiency, and risk of cardiovascular disease. Wilson disease is a rare inherited disorder of copper transport that results in low serum copper and ceruloplasmin, and accumulation of copper in various tissues. The pathological accumulation of copper in the liver, brain, cornea, and kidney cause cirrhosis, neuropsychiatric symptoms, Kayser-Fleischer rings, and hematuria/proteinuria, respectively. See Wilson Disease Testing Algorithm in Special Instructions for appropriate use of clinical findings, serum biomarkers, genetic tests, and tissue biopsies when working up suspected cases. Menkes disease is an X-linked disorder in which dietary copper is absorbed from the gastrointestinal tract but cannot be transported, so copper is not available to the liver for incorporation into ceruloplasmin. Dietary ceruloplasmin deficiency may be due to inadequate dietary copper intake, long-term parenteral nutrition without copper supplementation, malabsorption, penicillamine therapy, or a combination of these.

Useful For: Investigation of patients with possible Wilson disease

Interpretation: Low concentrations of ceruloplasmin are consistent with Wilson disease and warrant further investigation. Values vary considerably from patient to patient and may be in the normal range in some patients with Wilson disease (indicating a different primary defect). Ceruloplasmin is a positive acute-phase reactant. Increases in serum ceruloplasmin have been reported during pregnancy, in women taking oral contraceptives, in hepatitis, pneumonia, tuberculosis, rheumatoid arthritis, myocardial infarction, various forms of anemia, and many obscure neurological disorders.

Reference Values:
Males:
- 0-8 weeks: 7.4-23.7 mg/dL
- 9 weeks-5 months: 13.5-32.9 mg/dL
- 6-11 months: 13.7-38.9 mg/dL
- 12 months-7 years: 21.7-43.3 mg/dL
- 8-13 years: 20.5-40.2 mg/dL
- 14-17 years: 17.0-34.8 mg/dL
- > or =18 years: 19.0-31.0 mg/dL

CERS
113118
Females:
- 0-8 weeks: 7.4-23.7 mg/dL
- 9 weeks-5 months: 13.5-32.9 mg/dL
- 6-11 months: 13.7-38.9 mg/dL
- 12 months-7 years: 21.7-43.3 mg/dL
- 8-13 years: 20.5-40.2 mg/dL
- 14-17 years: 20.8-43.2 mg/dL
- > or = 18 years: 20.0-51.0 mg/dL

Clinical References:

CFTR Gene, Full Gene Analysis

Clinical Information: Cystic fibrosis (CF), in the classic form, is a severe autosomal recessive disorder characterized by a varied degree of chronic obstructive lung disease and pancreatic enzyme insufficiency. Clinical diagnosis is generally made based on these features, combined with a positive sweat chloride test or positive nasal potential difference. CF can also have an atypical presentation and may manifest as congenital bilateral absence of the vas deferens (CBAVD), chronic idiopathic pancreatitis, bronchiectasis, or chronic rhinosinusitis. Several states have implemented newborn screening for CF, which identifies potentially affected individuals by measuring immunoreactive trypsinogen in a dried blood specimen collected on filter paper. If a clinical diagnosis of CF has been made, molecular testing for common CF mutations is available. To date, over 1,500 mutations have been described within the CF gene, named cystic fibrosis transmembrane conductance regulator (CFTR). The most common mutation, deltaF508, accounts for approximately 67% of the mutations worldwide and approximately 70% to 75% in the North American Caucasian population. Most of the remaining mutations are rather rare, although some show a relatively higher prevalence in certain ethnic groups or in some atypical presentations of CF, such as isolated CBAVD. The recommended approach for confirming a CF diagnosis or detecting carrier status begins with molecular tests for the common CF mutations (eg, CFB / Cystic Fibrosis Mutation Analysis, 106-Mutation Panel). This test, CFTR Gene, Full Gene Analysis may be ordered if 1 or both disease-causing mutations are not detected by the targeted mutation analysis (CFB / Cystic Fibrosis Mutation Analysis, 106-Mutation Panel). Full gene analysis, sequencing and dosage analysis of the CFTR gene, is utilized to detect private mutations. Together, full gene analysis of the CFTR gene and deletion/duplication analysis identify over 98% of the sequence variants in the coding region and splice junctions. Of note, CFTR potentiator therapies may improve clinical outcomes for patients with a clinical diagnosis of CF and at least 1 copy of the G178R, G551S, G551D, S549N, S549R, G1244E, S1251N, S1255P, or G1349D mutation. See Cystic Fibrosis Molecular Diagnostic Testing Algorithm in Special Instructions for additional information.

Useful For: Follow-up testing to identify mutations in individuals with a clinical diagnosis of cystic fibrosis (CF) and a negative targeted mutation analysis for the common CF mutations. Identification of mutations in individuals with atypical presentations of CF (eg, congenital bilateral absence of the vas deferens or pancreatitis). Identification of mutations in individuals where detection rates by targeted mutation analysis are low or unknown for their ethnic background. Identification of patients who may respond to cystic fibrosis transmembrane conductance regulator (CFTR) potentiator therapy. This is not the preferred genetic test for carrier screening or initial diagnosis. For these situations, order CFB / Cystic Fibrosis Mutation Analysis, 106-Mutation Panel.

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.
Reference Values:
An interpretive report will be provided.


Chaetomium globosum, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.

**Cheese American IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

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**Cheese Cheddar IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation* 2.0 Upper Limit of Quantitation** 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

---

**Cheese Swiss IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

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**Cheese, Cheddar, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Cheese, Mold, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** May be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. May be useful to identify allergens that may be responsible for allergic disease or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<tbody>
<tr>
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<td>0.35-0.69</td>
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</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**CHEK2 Gene, Full Gene Analysis**

**Clinical Information:** Li-Fraumeni syndrome (LFS) is a rare autosomal dominant hereditary cancer syndrome associated with germline mutations in the TP53 (also p53) gene. LFS is predominantly characterized by sarcoma (osteogenic, chondrosarcoma, rhabdomyosarcoma), young-onset breast cancer, brain cancer (glioblastoma), hematopoietic malignancies, and adenocortical carcinoma in affected individuals. LFS is highly penetrant; the risk for developing an invasive cancer is 50% by age 30 and 90% by age 70 with many individuals developing multiple primary cancers. Childhood cancers are also frequently observed and typically include soft-tissue sarcomas, adenocortical tumors, and brain cancer. Other reported malignancies include melanoma, Wilms tumor, kidney tumors, gonadal germ cell tumor, pancreatic cancer, gastric cancer, choroid plexus cancer, colorectal cancer, prostate cancer, endometrial cancer, esophageal cancer, lung cancer, ovarian cancer, and thyroid cancer. Germline mutations in the CHEK2 gene have also been described in families with Li-Fraumeni-like (LFL) syndrome, which is characterized by similar tumor types but is associated with less stringent clinical criteria than Li-Fraumeni syndrome. Several studies have demonstrated an increased risk for breast cancer associated with founder mutations in CHEK2 (eg, c.1100delC). Two recent studies, a large association study(1) and a meta-analysis,(2) demonstrated an odds ratio of 2.7 to 3.6 for breast cancer in unselected breast cancer patients (without a family history) and an odds ratio of 4.8 to 5.0 for individuals with a family history of breast cancer in a first- and second-degree relative. This suggests a moderate increase in breast cancer risk in women with a truncating CHEK2 mutation without a family history of breast cancer. These studies also suggest that truncating CHEK2 mutations are modifiers of breast cancer risk in the context of a positive family history of breast cancer. Some studies have also suggested an increased risk for colorectal cancer associated with germline CHEK2 mutations; however, other studies have suggested that CHEK2 is not a major contributor to colorectal cancer risk. This test uses array comparative genomic hybridization (aCGH) to test for the presence of large deletions and duplications.

**Useful For:** Evaluation for hereditary susceptibility to breast cancer or Li-Fraumeni-like syndrome
Identification of a familial CHEK2 mutation to allow for predictive testing in family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(3) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Cherry, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<thead>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


Chestnut Tree, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Chestnut, Sweet, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


CHICF 35264

CHIC2 (4q12) Deletion (FIP1L1 and PDGFRA Fusion), FISH

Clinical Information: Imatinib mesylate, a small molecule tyrosine kinase inhibitor from the 2-phenylaminopyrimidine class of compounds, has shown activity in the treatment of malignancies that are associated with the constitutive activation of a specific subgroup of tyrosine kinases. A novel tyrosine kinase, generated from fusion of the Fip1-like 1 (FIP1L1) gene to the PDGFRA gene, was identified in 9 of 16 patients (56%) with hypereosinophilic syndrome (HES). This fusion results from an approximate 800 kb interstitial chromosomal deletion that includes the cysteine-rich hydrophobic domain 2 (CHIC2) locus at 4q12. FIP1L1-PDGFRα is a constitutively activated tyrosine kinase that transforms hematopoietic cells, and is a therapeutic target for imatinib in a subset of HES patients. Mast cell disease (MCD) is a clinically heterogeneous disorder wherein accumulation of mast cells (MC) may be limited to the skin (cutaneous mastocytosis) or involve 1 or more extra-cutaneous organs (systemic MCD [SMCD]). SMCD is often associated with eosinophilia (SMCD-eos). We recently tested the therapeutic activity of imatinib in 12 adults with SMCD-eos. In this study, we demonstrated that FIP1L1-PDGFRα is the therapeutic target of imatinib in the specific subset of patients with SMCD-eos. Furthermore, we provided evidence that the CHIC2 deletion is a surrogate marker for the FIP1L1-PDGFRα fusion.

Useful For: Providing genetic information for patients with hypereosinophilic syndrome (HES) and systemic mast cell disease (SMCD) involving CHIC2 deletion Identifying and tracking chromosome abnormalities and response to therapy

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range. Detection of an abnormal clone is usually associated with hypereosinophilic syndrome or systemic mastocytosis associated with eosinophilia. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

Reference Values:
An interpretive report will be provided.


CHXP 82494

Chick Pea, IgE
**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<th>IgE KU/L</th>
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<tr>
<td>0</td>
<td>0.35-0.69</td>
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<tr>
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<td>3</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>4</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


---

**Chicken Droppings, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease
and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Chicken Feathers, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
</tbody>
</table>
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


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**Chicken IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:** <2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**Chicken Serum Proteins, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

Class IgE kU/L Interpretation

CHIC 82703

Chicken, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class IgE kU/L Interpretation

0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.

**CHIKG 63868**

**Chikungunya IgG, Antibody, Serum**

**Reference Values:**
Only orderable as part of a profile. For more information see CHIKV / Chikungunya IgM and IgG, Antibody, Serum.

**CHIKV 64173**

**Chikungunya IgM and IgG, Antibody, Serum**

**Clinical Information:** Chikungunya virus (ChikV) is a single-stranded RNA alphavirus and a member of the Togaviridae family of viruses. The name Chikungunya is derived from the language of the Makonde ethnic groups in southeast Africa and means “that which bends” or “stooped walk.” This is in reference to the hunched-over appearance of infected individuals due to the characteristically painful and incapacitating arthralgia caused by the virus. ChikV is endemic throughout Africa, India, and more recently the Caribbean islands. In 2014, the first case of autochthonous or local transmission in the United States occurred in Florida. Humans are the primary reservoir for ChikV and Aedes species mosquitoes are the primary vectors for transmission. Unlike other mosquito-borne viruses such as West Nile virus (WNV) and Dengue, the majority of individuals who are exposed to ChikV become symptomatic, with the most severe manifestations observed at the extremes of age and in those with suppressed immunity. Once exposed to ChikV virus, individuals develop lasting immunity and protection from reinfection. The incubation period, prior to development of symptoms, ranges on average from 3 to 7 days. Infected patients typically present with sudden onset high fever, incapacitating joint pain, and often a maculopapular rash lasting anywhere from 3 to 10 days. Notably, symptom relapse can occur in some individuals 2 to 3 months following resolution of initial symptoms. Currently, there are no licensed vaccines and treatment is strictly supportive care.

**Useful For:** Aiding in the diagnosis of recent infection with Chikungunya virus in patients with recent travel to endemic areas and a compatible clinical syndrome

**Interpretation:** IgM and IgG Negative: -No serologic evidence of exposure to Chikungunya virus. Repeat testing on a new specimen collected in 5 to 10 days is recommended if clinical suspicion persists. IgM and IgG Positive: -IgM and IgG antibodies to Chikungunya virus detected, suggesting recent or past infection. IgM antibodies to Chikungunya virus may remain detectable for 3 to 4 months postinfection. IgM Positive, IgG Negative: -IgM antibodies to Chikungunya virus detected, suggesting recent infection. Repeat testing in 5 to 10 days is recommended to demonstrate anti-Chikungunya virus IgG seroconversion to confirm current infection. IgM Negative, IgG Positive: -IgG antibodies to Chikungunya virus detected, suggesting past infection. IgM and/or IgG Borderline: -Repeat testing in 10 to 14 days is recommended.

**Reference Values:**
IgM: Negative
IgG: Negative
Reference values apply to all ages.

**Clinical References:** Pan American Health Organization. Preparedness and Response for Chikungunya virus. Introduction into the Americas. Washington, DC, PAHO 2011

**CHIKM 63867**

**Chikungunya IgM, Antibody, Serum**

**Reference Values:**
Only orderable as part of a profile. For more information see CHIKV / Chikungunya IgM and IgG, Antibody, Serum.
Chikungunya Interpretation

Reference Values:
Only orderable as part of a profile. For more information see CHIKV / Chikungunya IgM and IgG, Antibody, Serum.

Chikungunya Virus RNA, Qualitative Real-Time PCR

Clinical Information: Chikungunya Virus is a mosquito-transmitted virus that is usually associated with acute epidemic polyarthralgia and fever. Detection of Chikungunya Virus by this assay is based upon the real-time amplification of viral genomic RNA sequences from total nucleic acid extracton of the specimen.

Reference Values:
Not Detected

Chili Pepper, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.
**Chimerism Transplant No Cell Sort**

**Clinical Information:** Patients who have had donor hematopoietic cells infused for the purpose of engraftment (ie, bone marrow transplant recipients) may have their blood or bone marrow monitored for an estimate of the percentage of donor and recipient cells present. This can be done by first identifying unique features of the donor's and the recipient's DNA prior to transplantation and then examining the recipient's blood or bone marrow after the transplantation procedure has occurred. The presence of both donor and recipient cells (chimerism) and the percentage of donor cells are indicators of transplant success. Short tandem repeat (STR) sequences are used as identity markers. STRs are di-, tri-, or tetra-nucleotide repeat sequences interspersed throughout the genome at specific sites. There is variability in STR length among people and the STR lengths remain stable throughout life, making them useful as identity markers. PCR is used to amplify selected STR regions from germline DNA of both donor and recipient. The lengths of the amplified fragment are evaluated for differences (informative markers). Following allogeneic hematopoietic cell infusion, the recipient blood or bone marrow can again be evaluated for the informative STR regions to identify chimerism and estimate the proportions of donor and recipient cells in the specimen.

**Useful For:** Determining the relative amounts of donor and recipient cells in a specimen An indicator of bone marrow transplant success

**Interpretation:** An interpretive report is provided, which defines unique features of the donor's cells. It is most useful to observe a trend in chimerism levels. Clinically critical results should be confirmed with 1 or more subsequent specimens.

**Reference Values:** An interpretive report will be provided.


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**Chimerism Transplant Sorted Cells**

**Clinical Information:** Patients who have had donor hematopoietic cells infused for the purpose of engraftment (ie, bone marrow transplant recipients) may have their blood or bone marrow monitored for an estimate of the percentage of donor and recipient cells present. This can be done by first identifying unique features of the donor's and the recipient's DNA prior to transplantation and then examining the recipient's blood or bone marrow after the transplantation procedure has occurred. The presence of both donor and recipient cells (chimerism) and the percentage of donor cells are indicators of transplant success. Short tandem repeat (STR) sequences are used as identity markers. STRs are di-, tri-, or tetra-nucleotide repeat sequences interspersed throughout the genome at specific sites. There is variability in STR length among people and the STR lengths remain stable throughout life, making them useful as identity markers. PCR is used to amplify selected STR regions from germline DNA of both donor and recipient. The lengths of the amplified fragment are evaluated for differences (informative markers). Following allogeneic hematopoietic cell infusion, the recipient blood or bone marrow can again be evaluated for the informative STR regions to identify chimerism and estimate the proportions of donor and recipient cells in the specimen.

**Useful For:** Determining the relative amounts of donor and recipient cells in a specimen in sorted cell fractions An indicator of bone marrow transplant success

**Interpretation:** An interpretive report is provided, which includes whether chimerism is detected or
not and, if detected, the approximate percentage of donor and recipient cells. Sorted cell analysis permits more detailed evaluation of chimeric status in T-cell and myeloid cell fractions, which can be helpful in clinical management. It is most useful to observe a trend in chimerism levels. Clinically critical results should be confirmed with 1 or more subsequent specimens.

**Reference Values:**
An interpretive report will be provided.


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**Chimerism-Donor**

**Clinical Information:** Patients who have had donor hematopoietic cells infused for the purpose of engraftment (ie, bone marrow transplant recipients) may have their blood or bone marrow monitored for an estimate of the percentage of donor and recipient cells present. This can be done by first identifying unique features of the donor's and the recipient's DNA prior to transplantation and then examining the recipient's blood or bone marrow after the transplantation procedure has occurred. The presence of both donor and recipient cells (chimerism) and the percentage of donor cells are indicators of transplant success. Short tandem repeat (STR) sequences are used as identity markers. STRs are di-, tri-, or tetra-nucleotide repeat sequences interspersed throughout the genome at specific sites. There is variability in STR length among people and the STR lengths remain stable throughout life, making them useful as identity markers. PCR is used to amplify selected STR regions from germline DNA of both donor and recipient. The lengths of the amplified fragment are evaluated for differences (informative markers). Following allogeneic hematopoietic cell infusion, the recipient blood or bone marrow can again be evaluated for the informative STR regions to identify chimerism and estimate the proportions of donor and recipient cells in the specimen. This test evaluates the donor specimen prior to the recipient bone marrow transplant.

**Useful For:** Evaluating the donor cells prior to bone marrow transplant Determining the relative amounts of donor and recipient cells in a specimen. An indicator of bone marrow transplant success

**Interpretation:** An interpretive report is provided, which includes whether chimerism is detected or not and, if detected, the approximate percentage of donor and recipient cells. Sorted cell analysis permits more detailed evaluation of chimeric status in T-cell and myeloid cell fractions, which can be helpful in clinical management. It is most useful to observe a trend in chimerism levels. Clinically critical results should be confirmed with 1 or more subsequent specimens.

**Reference Values:**
An interpretive report will be provided.


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**Chimerism-Recipient Germline (Pre)**

**Clinical Information:** Patients who have had donor hematopoietic cells infused for the purpose of engraftment (ie, bone marrow transplant recipients) may have their blood or bone marrow monitored for an estimate of the percentage of donor and recipient cells present. This can be done by first identifying unique features of the donor's and the recipient's DNA prior to transplantation and then examining the recipient's blood or bone marrow after the transplantation procedure has occurred. The presence of both donor and recipient cells (chimerism) and the percentage of donor cells are indicators of transplant success. Short tandem repeat (STR) sequences are used as identity markers. STRs are di-, tri-, or tetra-nucleotide repeat sequences interspersed throughout the genome at specific sites. There is variability in STR length among people and the STR lengths remain stable throughout life, making them useful as
identity markers. PCR is used to amplify selected STR regions from germline DNA of both donor and recipient. The lengths of the amplified fragment are evaluated for differences (informative markers). Following allogeneic hematopoietic cell infusion, the recipient blood or bone marrow can again be evaluated for the informative STR regions to identify chimerism and estimate the proportions of donor and recipient cells in the specimen. This CHRGB / Chimerism-Recipient Germline (Pre) orderable evaluates the recipient specimen prior to bone marrow transplant.

**Useful For:** Evaluating the recipient cells prior to bone marrow transplant

**Interpretation:** An interpretive report is provided, which includes whether chimerism is detected or not and, if detected, the approximate percentage of donor and recipient cells. Sorted cell analysis permits more detailed evaluation of chimeric status in T-cell and myeloid cell fractions, which can be helpful in clinical management. It is most useful to observe a trend in chimerism levels. Clinically critical results should be confirmed with 1 or more subsequent specimens.

**Reference Values:**
An interpretive report will be provided.


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**FCPP 57339**

**Chlamydia Pneumoniae PCR**

**Reference Values:**
Not detected = Negative, no virus detected
Detected = Positive, virus detected

This test employs PCR amplification and agarose gel electrophoresis detection of a Chlamydia pneumoniae-specific conserved genetic target. A positive result should be coupled with clinical indicators for diagnosis. A "Not detected" result for this assay does not exclude Chlamydia pneumoniae involvement in a disease process.

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**SCLAM 8142**

**Chlamydia Serology, Serum**

**Clinical Information:** Members of the family Chlamydiaceae are small, nonmotile, gram-negative, obligate intracellular organisms that grow in the cytoplasm of host cells. Two genera of clinical importance are Chlamydia, which includes Chlamydia trachomatis, and Chlamydophila, which includes Chlamydophila pneumoniae and Chlamydophila psittaci. These organisms share many features of bacteria and are susceptible to antibiotic therapy. They are also similar to viruses, requiring living cells for multiplication. The chlamydial life cycle can be divided into 2 distinct phases: an extracellular, nonreplicating, infectious stage and an obligate intracellular, replicating, noninfectious stage. The infectious form, or elementary body (EB), attaches to the target cell membrane and enters the cell via a phagosome. After cell entry, the EB reorganizes into reticulate particles (forming inclusion bodies) and binary fission begins. After 18 to 24 hours, reticulate particles condense to form EBs. These new EBs are released, beginning another infection cycle. Chlamydophila psittaci is the causative agent of psittacosis, a disease characterized by pneumonia, headache, altered mentation, and hepatosplenomegaly. Psittacosis is acquired by airborne transmission from infected birds. Chlamydophila pneumoniae (formerly known as TWAR and, more recently, as Chlamydia pneumoniae) causes pneumonia in humans. It is unique because it is a primary pathogen of humans, is spread from human to human, and apparently has no animal or bird host. Chlamydophila pneumoniae is responsible for approximately 10% of pneumonia cases. Chlamydia trachomatis has been implicated in a wide variety of infections in humans. It is a common cause of nongonococcal urethritis and cervicitis, and many systemic complications of chlamydial infections have been described. In females, this organism is a cause of pelvic inflammatory disease, salpingitis, and endometritis. In males, epididymitis and Reiter syndrome occur. Lymphogranuloma venereum is a sexually transmitted infection caused by Chlamydia trachomatis. It presents with a transient primary genital lesion followed by suppurative regional
lymphadenopathy. Occasionally, severe proctitis or proctocolitis may develop. Chlamydia trachomatis also causes ophthalmologic infections, such as trachoma (rare in the United States), adult inclusion conjunctivitis and inclusion conjunctivitis in neonates. These disorders have traditionally been diagnosed by cytologic detection or culture. However, molecular detection methods (CTRNA / Chlamydia trachomatis by Nucleic Acid Amplification [GEN-PROBE]) may now represent a more sensitive diagnostic approach. Fitz-Hugh-Curtis syndrome (perihepatitis) has been associated with chlamydiae.

Useful For: Aids in the clinical diagnosis of chlamydial infections

**Interpretation:** IgG: Chlamydia pneumoniae \( \geq 1:512 \) IgG endpoint titers of \( > \) or \( = 1:512 \) are considered presumptive evidence of current infection. \( < 1:512 \) and \( > \) or \( = 1:64 \) A single specimen endpoint titer of \( > \) or \( = 1:64 \) and \( < 1:512 \) should be considered evidence of infection at an undetermined time. A second specimen drawn 10 to 21 days after the original draw should be tested in parallel with the first. If the second specimen exhibits a titer \( > \) or \( = 1:512 \) or a 4-fold increase over that of the initial specimen, current (acute) infection is indicated. Unchanging titers \( > 1:64 \) and \( < 1:512 \) suggest past infection. \( < 1:64 \) IgG endpoint titers \( < 1:64 \) suggest that the patient does not have a current infection. These antibody levels may be found in patients with either no history of chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels. Chlamydia pneumoniae antibody is detectable in 25% to 45% of adults tested. Chlamydia psittaci and Chlamydia trachomatis \( > \) or \( = 1:64 \) IgG endpoint titers of \( > \) or \( = 1:64 \) are considered presumptive evidence of current infection. \( < 1:64 \) IgG endpoint titers \( < 1:64 \) suggest that the patient does not have a current infection. These antibody levels may be found in patients with either no history of chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels. IgM Chlamydia pneumoniae, Chlamydia psittaci, and Chlamydia trachomatis \( > \) or \( = 1:10 \) IgM endpoint titers of \( > \) or \( = 1:10 \) are considered presumptive evidence of infection. \( < 1:10 \) IgM endpoint titers \( < 1:10 \) suggest that the patient does not have a current infection. These antibody levels may be found in patients with either no history of chlamydial infection or those with past infection whose antibody levels have dropped below detectable levels.

**Reference Values:**

Chlamydia pneumoniae

IgG: \( < 1:64 \)

IgM: \( < 1:10 \)

Chlamydia psittaci

IgG: \( < 1:64 \)

IgM: \( < 1:10 \)

Chlamydia trachomatis

IgG: \( < 1:64 \)

IgM: \( < 1:10 \)


**CGRNA 61553**

**Chlamydia trachomatis and Neisseria gonorrhoeae by Nucleic Acid Amplification (HOLOGIC)**

**Clinical Information:** Chlamydia is caused by the obligate intracellular bacterium Chlamydia trachomatis and is the most prevalent sexually transmitted bacterial infection (STI) in the United States.(1,2) In 2010, 1.3 million documented cases were reported to the CDC.(2) Given that 3 out of 4 infected women and 1 out of 2 infected men will be asymptomatic initially, the actual prevalence of disease is thought to be much greater than reported.(2) The organism causes genitourinary infections in
women and men and may be associated with dysuria and vaginal, urethral, or rectal discharge. In women, complications include pelvic inflammatory disease, salpingitis, and infertility. Approximately 25% to 30% of women who develop acute salpingitis become infertile. Complications among men are rare, but include epididymitis and sterility. Rarely, genital chlamydial infection can cause arthritis with associated skin lesions and ocular inflammation (Reiter syndrome). C trachomatis can be transmitted from the mother during delivery and is associated with conjunctivitis and pneumonia. Finally, C trachomatis may cause hepatitis and pharyngitis in adult. Once detected, the infection is easily treated by a short course of antibiotic therapy. Annual Chlamydia screening is now recommended for all sexually active women age 25 years and younger, and for older women with risk factors for infection, such as a new sex partner or multiple sex partners. The CDC also recommends that all pregnant women be given a screening test for chlamydia infection. Repeat testing for test-of-cure is not recommended after treatment with a standard treatment regimen unless patient compliance is in question, reinfection is suspected, or the patient's symptoms persist. Repeat testing of pregnant women, 3 weeks after completion of therapy, is also recommended to ensure therapeutic cure. Gonorrhea is caused by the bacterium Neisseria gonorrhoeae. It is also a very common STI, with 301,174 cases of gonorrhea reported to CDC in 2009. Like Chlamydia, many infections in women are asymptomatic, and the true prevalence of gonorrhea is likely much higher than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria and vaginal, urethral, or rectal discharge. Complications include pelvic inflammatory disease in women and gonococcal epididymitis and prostatitis in men. Gonococcal bacteremia, pharyngitis, and arthritis may also occur. Infection in men is typically associated with symptoms that would prompt clinical evaluation. Given the risk for asymptomatic infection in women, screening is recommended for women at increased risk of infection (eg, women with previous gonorrhea or other STI, inconsistent condom use, new or multiple sex partners, and women in certain demographic groups such as those in communities with high STI prevalence.) The CDC currently recommends dual antibiotic treatment due to emerging antimicrobial resistance. Culture was previously considered to be the gold standard test for diagnosis of C trachomatis and N gonorrhoeae infection. However, these organisms are labile in vitro, and precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now the recommended method for diagnosis in most cases. Immunoassays and nonamplification DNA tests are also available for C trachomatis and N gonorrhoeae detection, but these methods are significantly less sensitive and less specific than NAATs. Improved screening rates and increased sensitivity of NAAT testing have resulted in an increased number of accurately diagnosed cases. Improved detection rates result from both the increased performance of the assay and the patients' easy acceptance of urine testing. Early identification of infection enables sexual partners to seek testing and/or treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

**Useful For:** Detection of Chlamydia trachomatis or Neisseria gonorrhoeae

**Interpretation:** A positive result indicates that rRNA of Chlamydia trachomatis or Neisseria gonorrhoeae is present in the specimen tested and strongly supports a diagnosis of chlamydial or gonorrheal infection. A negative result indicates that rRNA for C trachomatis or N gonorrhoeae was not detected in the specimen. The predictive value of an assay depends on the prevalence of the disease in any particular population. In settings with a high prevalence of sexually transmitted disease, positive assay results have a high likelihood of being true-positives. In settings with a low prevalence of sexually transmitted disease, or in any setting in which a patient's clinical signs and symptoms or risk factors are inconsistent with gonococcal or chlamydial urogenital infection, positive results should be carefully assessed and the patient retested by other methods (eg, culture for N gonorrhoeae), if appropriate. A negative result does not exclude the possibility of infection. If clinical indications strongly suggest gonococcal or chlamydial infection, additional specimens should be collected for testing. A result of indeterminate indicates that a new specimen should be collected. This test has not been shown to cross react with commensal (nonpathogenic) Neisseria species present in the oropharynx.

**Reference Values:**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia trachomatis</td>
<td>Negative</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td></td>
</tr>
</tbody>
</table>
**Clinical References:**


**Chlamydia trachomatis by Nucleic Acid Amplification (HOLOGIC)**

**Clinical Information:**
Chlamydia is caused by the obligate intracellular bacterium Chlamydia trachomatis and is the most prevalent sexually transmitted bacterial infection (STI) in the United States.(1,2) In 2010, 1.3 million documented cases were reported to the Centers for Disease Control and Prevention (CDC). (2) Given that 3 out of 4 infected women and 1 out of 2 infected men will be asymptomatic initially, the actual prevalence of disease is thought to be much greater than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria and vaginal, urethral, or rectal discharge. In women, complications include pelvic inflammatory disease, salpingitis, and infertility. Approximately 25% to 30% of women who develop acute salpingitis become infertile.(2) Complications among men are rare, but include epididymitis and sterility. Rarely, genital chlamydial infection can cause arthritis with associated skin lesions and ocular inflammation (Reiter syndrome). C trachomatis can be transmitted from the mother during deliver and is associated with conjunctivitis and pneumonia. Finally, C trachomatis may cause hepatitis and pharyngitis in adults. Once detected, the infection is easily treated by a short course of antibiotic therapy. Annual chlamydia screening is now recommended for all sexually active women age 25 years and younger, and for older women with risk factors for infection, such as a new sex partner or multiple sex partners. The CDC also recommends that all pregnant women be given a screening test for Chlamydia infection.(2) Repeat testing for test-of-cure is not recommended after treatment with a standard treatment regimen unless patient compliance is in question, reinfection is suspected, or the patient's symptoms persist. Repeat testing of pregnant women, 3 weeks after completion of therapy, is also recommended to ensure therapeutic cure.(2) Culture was previously considered to be the gold standard test for diagnosis of C trachomatis infection. However, organisms are labile in vitro, and precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now the recommended method for diagnosis in most cases.(3-5) Immunoassays and nonamplification DNA tests are also available for C trachomatis detection, but these methods are significantly less sensitive and less specific than NAATs.(2) Improved screening rates and increased sensitivity of NAAT testing have resulted in an increased number of accurately diagnosed cases.(2) Improved detection rates result from both the increased performance of the assay. Early identification of infection enables sexual partners to seek testing and/or treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

**Useful For:** Detection of Chlamydia trachomatis

**Interpretation:** A positive result indicates the presence of rRNA Chlamydia trachomatis. A negative result indicates that rRNA for C trachomatis was not detected in the specimen. The predictive value of an assay depends on the prevalence of the disease in any particular population. In settings with a high prevalence of sexually transmitted disease, positive assay results have a high likelihood of being true-positives. In settings with a low prevalence of sexually transmitted disease, or in any setting in which a patient's clinical signs and symptoms or risk factors are inconsistent with chlamydial or gonococcal
urogenital infection, positive results should be carefully assessed and the patient retested by other methods, if appropriate.

Reference Values:
Negative


Chlamydia trachomatis, Miscellaneous Sites, by Nucleic Acid Amplification

Clinical Information: Chlamydia is caused by the obligate intracellular bacterium Chlamydia trachomatis and is the most prevalent sexually transmitted bacterial infection in the United States.(1,2) In 2010, 1.3 million documented cases were reported to the CDC.(2) Given that 3 out of 4 infected women and 1 out of 2 infected men will be asymptomatic initially, the actual prevalence of disease is thought to be much greater than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria and vaginal, urethral, or rectal discharge. In women, complications include pelvic inflammatory disease, salpingitis, and infertility. Approximately 25% to 30% of women who develop acute salpingitis become infertile.(2) Complications among men are rare, but include epididymitis and sterility. Rarely, genital chlamydial infection can cause arthritis with associated skin lesions and ocular inflammation (Reiter syndrome). C trachomatis can be transmitted from the mother during delivery and is associated with conjunctivitis and pneumonia. Finally, C trachomatis may cause hepatitis and pharyngitis in adults. Once detected, the infection is easily treated by a short course of antibiotic therapy. Annual chlamydia screening is now recommended for all sexually active women age 25 years and younger, and for older women with risk factors for infection, such as a new sex partner or multiple sex partners. The CDC also recommends that all pregnant women be given a screening test for Chlamydia infection.(2) Repeat testing for test-of-cure is not recommended after treatment with a standard treatment regimen unless patient compliance is in question, reinfection is suspected, or the patient's symptoms persist. Repeat testing of pregnant women, 3 weeks after completion of therapy, is also recommended to ensure therapeutic cure.(2) Culture was previously considered to be the gold standard test for diagnosis of C trachomatis infection.(2) However, organisms are labile in vitro, and precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now the recommended method for diagnosis in most cases.(3-5) Immunoassays and nonamplification DNA tests are also available for C trachomatis detection, but these methods are significantly less sensitive and less specific than NAAT.(2) Improved screening rates and increased sensitivity of NAAT testing have resulted in an increased number of accurately diagnosed cases.(2) Early identification of infection enables sexual partners to seek testing and treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

Useful For: Detection of Chlamydia trachomatis in non-FDA-approved specimen types

Interpretation: A positive result indicates the presence of rRNA Chlamydia trachomatis. This assay does detect plasmid-free variants of C trachomatis. A negative result indicates that rRNA for C trachomatis was not detected in the specimen. The predictive value of an assay depends on the
prevalence of the disease in any particular population. In settings with a high prevalence of sexually transmitted disease, positive assay results have a high likelihood of being true positives. In settings with a low prevalence of sexually transmitted disease, or in any setting in which a patient’s clinical signs and symptoms or risk factors are inconsistent with chlamydial urogenital infection, positive results should be carefully assessed and the patient retested by other methods, if appropriate.

Reference Values:
Negative


Chlamydia pneumoniae DNA, Qualitative Real-Time PCR

Clinical Information: This test is used to determine the presence of Chlamydia pneumoniae in a patient’s specimen. Organisms may be detected by PCR prior to detection by immunological methods. PCR provides more rapid results than other methods, including culture.

Reference Values:
Reference Range: Not Detected

Chlordane and Metabolites, Serum/Plasma

Reference Values:
Reporting limit determined each analysis

Alpha-Chlordane
Synonym(s): Cis-Chlordane
Results reported in ppb

Gamma-Chlordane
Synonym(s): Trans-Chlordane
Results reported in ppb

Trans-Nonachlor
Synonym(s): Chlordane Component
Results reported in ppb

Heptaclorepoxide
Synonym(s): Chlordane Metabolite
Results reported in ppb

Oxychlordane
Synonym(s): Chlordane Metabolite
Results reported in ppb

Heptchlor
Chlordiazepoxide and Metabolite, Serum

Clinical Information: Chlordiazepoxide (Librium) is a benzodiazepine widely used in the treatment of anxiety, alcohol withdrawal symptoms, and as a premedication for anesthesia. The mechanism of action of all benzodiazepines remains unclear. However, it is known that benzodiazepines facilitate gamma-amino butyric acid (GABA)-mediated neurotransmission in the brain. Benzodiazepines most likely facilitate the inhibitory presynaptic or postsynaptic reactions of GABA. Chlordiazepoxide is metabolized to long-acting metabolites in the liver to the active metabolite nordiazepam (desmethyldiazepam) and the clearance of the drug is reduced considerably in the elderly and in patients with hepatic disease. Therapeutic assessment should include measurement of both the parent drug (chlordiazepoxide) and the active metabolite (nordiazepam). Since chlordiazepoxide has a wide therapeutic index and toxicity is dose-dependent, routine drug monitoring is not indicated in all patients.

Useful For: Monitoring chlordiazepoxide therapy Assessing toxicity

Interpretation: Chlordiazepoxide and nordiazepoxide combined concentrations above 5000 ng/mL have been associated with toxicity.

Reference Values:
Therapeutic concentration:
  Chlordiazepoxide: 400-3,000 ng/mL
  Nordiazepam: 100-500 ng/mL


Chloride, 24 Hour, Urine

Clinical Information: Chloride is the major extracellular anion. Its precise function in the body is not well understood; however, it is involved in maintaining osmotic pressure, proper body hydration, and electric neutrality. In the absence of acid-base disturbances, chloride concentrations in plasma will generally follow those of sodium (Na+). Since urine is the primary mode of elimination of ingested chloride, urinary chloride excretion during steady state conditions will reflect ingested chloride, which predominantly is in the form of sodium chloride (NaCl). However, under certain clinical conditions, the renal excretion of chloride may not reflect intake. For instance, during states of extracellular volume depletion, urine chloride (and sodium) excretion is reduced.

Useful For: An indicator of fluid balance and acid-base homeostasis

Interpretation: Urine sodium and chloride excretion are similar and, under steady-state conditions, both the urinary sodium and chloride excretion reflect the intake of sodium chloride (NaCl). During states of extracellular volume depletion, low values indicate appropriate renal reabsorption of these ions, whereas elevated values indicate inappropriate excretion (renal wasting). Urinary sodium and chloride excretion may be dissociated during metabolic alkalosis with volume depletion where urine sodium excretion may be high (due to renal excretion of NaHCO3), while urine chloride excretion remains appropriately low.
**Chloride, Body Fluid**

**Reference Values:**
Not applicable

**Clinical References:**

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**Chloride, Random, Urine**

**Clinical Information:**
Chloride is the major extracellular anion. Its precise function in the body is not well understood; however, it is involved in maintaining osmotic pressure, proper body hydration, and electric neutrality. In the absence of acid-base disturbances, chloride concentrations in plasma will generally follow those of sodium (Na+). Since urine is the primary mode of elimination of ingested chloride, urinary chloride excretion during steady state conditions will reflect ingested chloride, which predominantly is in the form of sodium chloride (NaCl). However, under certain clinical conditions, the renal excretion of chloride may not reflect intake. For instance, during states of extracellular volume depletion, urine chloride (and sodium) excretion is reduced.

**Useful For:** An indicator of fluid balance and acid-base homeostasis

**Interpretation:** Urine sodium and chloride excretion are similar and, under steady state conditions, both the urinary sodium and chloride excretion reflect the intake of sodium chloride (NaCl). During states of extracellular volume depletion, low values indicate appropriate renal reabsorption of these ions, whereas elevated values indicate inappropriate excretion (renal wasting). Urinary sodium and chloride excretion may be dissociated during metabolic alkalosis with volume depletion where urine sodium excretion may be high (due to renal excretion of NaHCO3) while urine chloride excretion remains appropriately low.

**Reference Values:**
Interpret with other clinical data.

**Clinical References:**

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**Chloride, Serum**

**Clinical Information:**
Chloride is the major anion in the extracellular water space; its physiological significance is in maintaining proper body water distribution, osmotic pressure, and normal anion-cation balance in the extracellular fluid compartment. Chloride is increased in dehydration, renal tubular acidosis (hyperchloremia metabolic acidosis), acute renal failure, metabolic acidosis associated with prolonged diarrhea and loss of sodium bicarbonate, diabetes insipidus, adrenocortical hyperfunction, salicylate intoxication, and with excessive infusion of isotonic saline or extremely high dietary intake of salt. Hyperchloremia acidosis may be a sign of severe renal tubular pathology. Chloride is decreased in...
overhydration, chronic respiratory acidosis, salt-losing nephritis, metabolic alkalosis, congestive heart failure, Addisonian crisis, certain types of metabolic acidosis, persistent gastric secretion and prolonged vomiting, aldosteronism, bromide intoxication, syndrome of inappropriate antidiuretic hormone secretion, and conditions associated with expansion of extracellular fluid volume.

**Useful For:** Evaluation of water, electrolyte, and acid-base status

**Interpretation:** In normal individuals, serum chloride values vary little during the day, although there is a slight decrease after meals due to the diversion of chloride to the production of gastric juice.

**Reference Values:**
1-17 years: 102-112 mmol/L
> or =18 years: 98-107 mmol/L
Reference values have not been established for patients who are under 12 months of age.

**Clinical References:** Tietz Textbook of Clinical Chemistry. Edited by CA Burtis, ER Ashwood. WB Saunders Company, Philadelphia, PA, 1994

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**Chloride, Spinal Fluid**

**Clinical Information:** Cerebrospinal fluid, which cushions the brain and spinal cord, is formed by both ultrafiltration and active secretion from plasma.

**Useful For:** This test is of limited clinical utility.

**Interpretation:** Cerebrospinal fluid chloride levels generally reflect systemic (blood) chloride levels.

**Reference Values:**
120-130 mmol/L

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**Chlorpromazine (Thorazine)**

**Reference Values:**
Reference Range: 30 â€“ 300 ng/mL

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**Chocolate/Cacao IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of the quantitation for the assay. The clinical utility of food-specific IgG test has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**Cholecystokinin (CCK)**

**Clinical Information:** Cholecystokinin is a 33 amino acid peptide having a very similar structure to Gastrin. Cholecystokinin is present in several different sized forms including a 58 peptide Pro-CCK and 22, 12, and 8 peptide metabolites. The octapeptide retains full activity of the 33 peptide molecule. Cholecystokinin has an important physiological role in the regulation of pancreatic secretion, gallbladder contraction and intestinal motility. Cholecystokinin levels are elevated by dietary fat especially in
diabetics. Elevated levels are seen in hepatic cirrhosis patients. Cholecystokinin is found in high levels in the gut, in the brain and throughout the central nervous system.

Reference Values:
Up to 80 pg/mL

This test was developed and its performance characteristics determined by Inter Science Institute. It has not been cleared or approved by the US Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

CHLBF
82945

Cholesterol, Body Fluid

Clinical Information: Pleural Fluid: Quantitation of cholesterol in body fluids is clinically important and relevant in particular to the diagnosis of a cholesterol effusion. Cholesterol effusions (also known as pseudochylothorax or chyliform effusion) are important to differentiate from chylothorax, as their etiologies and therapeutic management strategies differ. Pseudochylous or chyliform effusions accumulate gradually through the breakdown of cellular lipids in long-standing effusions such as rheumatoid pleuritis, tuberculosis, or myxedema, and by definition the effluent contains high concentrations of cholesterol. The fluid may have a milky or opalescent appearance and be similar to that of a chylous effusion, which contains high concentrations of triglycerides in the form of chylomicrons. An elevated cholesterol above 250 mg/dL defines a cholesterol effusion in pleural fluid. Peritoneal Fluid: Ascites is the pathologic accumulation of excess fluid in the peritoneal cavity. Cholesterol analysis in peritoneal fluid may be a useful index to separate malignant ascites (>45-48 mg/dL) from cirrhotic ascites. Using a cutoff value of 48 mg/dL, the sensitivity, specificity, positive and negative predictive value, and overall diagnostic accuracy for differentiating malignant from nonmalignant ascites were reported as 96.5%, 96.6%, 93.3%, 98.3%, and 96.6%, respectively. (1) Synovial Fluid: Normal synovial fluid contains extremely low concentrations of lipids. Abnormalities in synovial fluid lipids may be attributed to cholesterol-rich pseudochylous effusions, which may be associated with chronic rheumatoid arthritis, lipid droplets due to traumatic injury and rarely due to severe chylous effusions associated with systemic lupus erythematosus, filariasis, pancreatitis, and trauma. (1) However, these diseases can usually be differentiated clinically and by gross and microscopic examination; quantification of lipids in synovial fluid only provides supporting information to the clinical picture.

Useful For: Distinguishing between chylous and nonchylous effusions Identifying iatrogenic effusions

Interpretation: Not applicable

Reference Values: Not applicable

Clinical References:

HDCH
8429

Cholesterol, High-Density Lipoprotein (HDL), Serum

Clinical Information: High-density lipoprotein (HDL) is the smallest of the lipoprotein particles and comprises a complex family of lipoprotein particles that exist in a constant state of dynamic flux as the particles interact with other HDL particles and with low-density lipoprotein (LDL) particles and very-low-density lipoprotein (VLDL) particles. HDL has the largest proportion of protein relative to lipid compared to other lipoproteins (>50% protein). Total cholesterol levels have long been known to be related to coronary heart disease (CHD). HDL cholesterol is also an important tool used to assess an individual's risk of developing CHD since a strong negative relationship between HDL cholesterol
concentration and the incidence of CHD has been reported. In some individuals, exercise increases the HDL cholesterol level; those with more physical activity have higher HDL cholesterol values.

**Useful For:** Cardiovascular risk assessment

**Interpretation:** Low high-density lipoprotein (HDL) cholesterol correlates with increased risk for coronary heart disease (CHD). Values greater than or equal to 80 to 100 mg/dL may indicate metabolic response to certain medications such as hormone replacement therapy, chronic liver disease, or some form of chronic intoxication, such as with alcohol, heavy metals, or industrial chemicals including pesticides. HDL values of 5 mg/dL or less occur in Tangier disease, in association with cholestatic liver disease, and in association with diminished hepatocyte function.

**Reference Values:**
The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for lipids (total cholesterol, triglycerides, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and non-HDL cholesterol) in adults ages 18 and up:

- **HDL CHOLESTEROL**
  - Males: > or =40 mg/dL
  - Females: > or =50 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in children ages 2-17:

- **HDL CHOLESTEROL**
  - Low HDL: <40 mg/dL
  - Borderline low: 40-45 mg/dL
  - Acceptable: >45 mg/dL

**Clinical References:**

**CHOL**

**Cholesterol, Total, Serum**

**Clinical Information:** Cholesterol is a steroid with a secondary hydroxyl group in the C3 position. It is synthesized in many types of tissue, but particularly in the liver and intestinal wall. Approximately 75% of cholesterol is newly synthesized and 25% originates from dietary intake. Normally, the cholesterol in the plasma or serum is 60% to 80% esterified. Approximately 50% to 75% of the plasma cholesterol is transported by low-density lipoproteins (LDL) and 15% to 40% by high-density lipoproteins (HDL). Serum cholesterol is elevated in the hereditary hyperlipoproteinemias and in various other metabolic diseases. Moderate-to-markedly elevated values are also seen in cholestatic liver disease. Hypercholesterolemia reflects an increase of lipoproteins of 1 or more specific classes (eg, beta-LDL, alpha-1 HDL, alpha-2 HDL, or LP-X). Hypercholesterolemia is a risk factor for cardiovascular disease. Low levels of cholesterol can be seen in disorders that include hyperthyroidism, malabsorption, and deficiencies of apolipoproteins.

**Useful For:** Evaluation of cardiovascular risk

**Interpretation:** The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for total cholesterol: Desirable: <200 mg/dL Borderline high: 200 to 239 mg/dL High: > or =240 mg/dL Values above the normal range indicate a need for
quantitative analysis of the lipoprotein profile. Values in hyperthyroidism usually are in the lower normal range; malabsorption values may be below 100 mg/dL, while beta-lipoprotein or apolipoprotein B deficiency values usually are below 80 mg/dL. See Lipids and Lipoproteins in Blood Plasma (Serum) in Special Instructions.

Reference Values:
The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for lipids (total cholesterol, triglycerides, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and non-HDL cholesterol) in adults ages 18 and up:

**TOTAL CHOLESTEROL**
- Desirable: <200 mg/dL
- Borderline high: 200-239 mg/dL
- High: > or =240 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in children 2 to 17 years of age:

**TOTAL CHOLESTEROL**
- Acceptable: <170 mg/dL
- Borderline high: 170-199 mg/dL
- High: > or =200 mg/dL

Clinical References:

CHLE

**Cholesteryl Esters, Serum**

**Clinical Information:** Cholesterol in the blood serum normally is 60% to 80% esterified with fatty acids, largely as a result of the action of the enzyme lecithin-cholesterol acyltransferase (LCAT), which circulates in the blood in association with the high-density lipoproteins. LCAT transfers an acyl group for lecithin to cholesterol. Familial deficiency of LCAT is uncommon, usually occurring individuals of northern Europe descent, and is associated with erythrocyte abnormalities (target cells) and decreased (20% or less) esterification of plasma cholesterol. This is associated with early atherosclerosis, corneal opacification, hyperlipidemia, and mild hemolytic anemia. Persons with liver disease may have impaired formation of LCAT and, therefore, a secondary deficiency of this enzyme and of esterified plasma cholesterol.

**Useful For:** Establishing a diagnosis of lecithin-cholesterol acyltransferase deficiency Evaluating the extent of metabolic disturbance by bile stasis or liver disease

**Interpretation:** In patients with lecithin-cholesterol acyltransferase deficiency, the concentration of unesterified cholesterol in serum may increase 2 to 5 times the normal value, resulting in a decrease in esterified serum cholesterol to 20% or less of the total serum cholesterol.

**Reference Values:**
- 60-80% of total cholesterol
- Reference values have not been established for patients that are <16 years of age.

Chromatin (Nucleosomal) Antibody

Reference Values:
Reference Range: <1.0 Negative AI

Chromium for Occupational Monitoring, Urine

Clinical Information: Chromium (Cr) has an atomic mass of 51.996, atomic number 24, and valences ranging from 2(-) to 6(+). Hexavalent chromium, Cr(+6), and trivalent chromium, Cr(+3), are the 2 most prevalent forms. Cr(+3) is the only oxidation state present under normal physiologic conditions. Cr(+6) is widely used in industry to make chromium alloys including stainless steel pigments and electroplated coatings. Cr(+6), a known carcinogen, is rapidly metabolized to Cr(+3). Cr(+3) is the only form present in human urine.

Useful For: Screening for occupational exposure

Interpretation: The National Institute for Occupational Safety and Health (NIOSH) draft document on occupational exposure reviews the data supporting use of urine to assess chromium exposure.(1) They recommend a Biological Exposure Index of 10 mcg/g creatinine and 30 mcg/g creatinine for the increase in urinary chromium concentrations during a work shift and at the end of shift at the end of the workweek, respectively (Section 3.3.1).

Reference Values:
Chromium/creatinine ratio: <10.0 mcg/g creatinine


Chromium, 24 Hour, Urine

Clinical Information: Chromium (Cr) exists in valence states ranging from 2(-) to 6(+). Hexavalent chromium (Cr(+6)) and trivalent chromium (Cr(+3)) are the 2 most prevalent forms. Cr(+6) is used in industry to make chromium alloys including stainless steel, pigments, and electroplated coatings. Cr(+6), a known carcinogen, is immediately converted to Cr(+3) upon exposure to biological tissues. Cr(+3) is the only chromium species found in biological specimens. Urine chromium concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Screening for occupational exposure to chromium Monitoring metallic prosthetic implant wear

Interpretation: Chromium is principally excreted in the urine. Urine levels correlate with exposure. Results greater than the reference range indicate either recent exposure to chromium or specimen contamination during collection. Prosthesis wear is known to result in increased circulating concentration of metal ions. Modest increase (8-16 mcg/24 hour) in urine chromium concentration is likely to be associated with a prosthetic device in good condition. Urine concentrations >20 mcg/24 hour in a patient with chromium-based implant suggest significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure. The National Institute for Occupational Safety and Health (NIOSH) draft document on occupational exposure reviews the data supporting use of urine to assess chromium.
exposure. They recommend a Biological Exposure Index of 10 mcg/g creatinine and 30 mcg/g creatinine for the increase in urinary chromium concentrations during a work shift and at the end of shift at the end of the workweek, respectively. A test for this specific purpose (CHROMU / Chromium for Occupational Monitoring, Urine) is available.

**Reference Values:**
- 0-15 years: not established
- > or =16 years: 0.0-7.9 mcg/specimen

**Clinical References:**
2. NIOSH Hexavalent Chromium Criteria Document Update, September 2008; Available from URL: http://www.cdc.gov/niosh/topics/hexchrom/

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**Chromium, Blood**

**Clinical Information:** Chromium (Cr) is a naturally occurring element widely distributed in the environment. Chromium exists in several valence states with the 3 main forms being Cr(0), Cr(III), and Cr(VI). Cr(III) is an essential trace element that enhances the action of insulin. Deficiency leads to impaired growth, reduced life span, corneal lesions, and alterations in carbohydrates, lipid, and protein metabolism. Chromium is widely used in manufacturing processes to make various metal alloys such as stainless steel. It is also used in many consumer products including: wood treated with copper dichromate, leather tanned with chromic sulfate, and metal-on-metal hip replacements. The general population is most likely to be exposed to trace levels of chromium in the food that is eaten. Low levels of Cr(III) occur naturally in a variety of foods, such as fruits, vegetables, nuts, beverages, and meats. The highest potential occupational exposure occurs in the metallurgy and tanning industries, where workers may be exposed to high air concentrations. Per FDA recommendations, orthopedic surgeons should consider measuring and following serial chromium concentrations in EDTA anticoagulated whole blood in symptomatic patients with metal-on-metal hip implants as part of their overall clinical evaluation. Blood Cr concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Monitor exposure to chromium Monitoring metallic prosthetic implant wear

**Interpretation:** Results greater than the reference range indicate exposure to chromium (Cr) (see Cautions about specimen collection). Prosthesis wear is known to result in increased circulating concentration of metal ions. Increased blood trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

**Reference Values:**
- 0-17 years: not established
- > or =18 years: <1.0 ng/mL

**Clinical References:**
Chromium, Random, Urine

**Clinical Information:** Chromium (Cr) exists in valence states ranging from 2(-) to 6(+). Hexavalent chromium (Cr[+6]) and trivalent chromium (Cr[+3]) are the 2 most prevalent forms. Cr(+6) is used in industry to make chromium alloys including stainless steel, pigments, and electroplated coatings. Cr(+6), a known carcinogen, is immediately converted to Cr(+3) upon exposure to biological tissues. Cr(+3) is the only chromium species found in biological specimens. Urine chromium concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Screening for occupational exposure to chromium Monitoring metallic prosthetic implant wear

**Interpretation:** Chromium is principally excreted in the urine. Urine levels correlate with exposure. Results greater than the reference range indicate either recent exposure to chromium or specimen contamination during collection. Prosthesis wear is known to result in increased circulating concentration of metal ions. Modest increase (8-16 mcg/L) in urine chromium concentration is likely to be associated with a prosthetic device in good condition. Urine concentrations >20 mcg/L in a patient with chromium-based implant suggest significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure. The National Institute for Occupational Safety and Health (NIOSH) draft document on occupational exposure reviews the data supporting use of urine to assess chromium exposure. They recommend a Biological Exposure Index of 10 mcg/g creatinine and 30 mcg/g creatinine for the increase in urinary chromium concentrations during a work shift and at the end of shift at the end of the workweek, respectively. A test for this specific purpose (CHROMU / Chromium for Occupational Monitoring, Urine) is available.

**Reference Values:**
No established reference values


Chromium, Serum

**Clinical Information:** Chromium (Cr) exists in valence states ranging from 2(-) to 6(+). Hexavalent chromium (Cr[+6]) and trivalent chromium (Cr[+3]) are the 2 most prevalent forms. Cr(+6) is used in industry to make chromium alloys including stainless steel, pigments, and electroplated coatings. Cr(+6), a known carcinogen, is immediately converted to Cr(+3) upon exposure to biological tissues. Cr(+3) is the only chromium species found in biological specimens. Serum Cr concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Screening for occupational exposure Monitoring metallic prosthetic implant wear
Interpretation: Results greater than the flagged value indicate clinically significant exposure to chromium (Cr) (see Cautions about specimen collection). The reported units of measurement for chromium of ng/mL is equivalent to mcg/L. Prosthesis wear is known to result in an increased circulating concentration of metal ions. A modest increase (0.3-0.6 ng/mL) in serum Cr concentration is likely to be associated with a prosthetic device in good condition. Serum concentrations above 1 ng/mL in a patient with a Cr-based implant suggest significant prosthesis wear. Increased serum trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure. However, the FDA recommends testing chromium in EDTA anticoagulated whole blood in symptomatic patients with metal-on-metal implants.

Reference Values:

<0.3 ng/mL
When collected by a phlebotomist experienced in ultra-clean collection technique and handled according to the instructions in Trace Metals Analysis Specimen Collection and Transport in Special Instructions, we have observed the concentration of chromium in serum to be <0.3 ng/mL. However, the majority of specimens submitted for analysis from unexposed individuals contain 0.3 ng/mL to 0.9 ng/mL of chromium. Commercial evacuated blood collection tubes not designed for trace-metal specimen collection yield serum containing 2.0 ng/mL to 5.0 ng/mL chromium derived from the collection tube.


Chromogenic Factor IX Activity Assay, Plasma

Clinical Information: Factor IX (FIX) is a vitamin K-dependent serine protease synthesized in the liver and participates in the intrinsic coagulation pathway. Its biological half-life is 18 to 24 hours. Congenital FIX deficiency is inherited as an X-linked recessive bleeding disorder (hemophilia B). Severe deficiency (<1%) characterized by hemarthroses, deep tissue bleeding, excessive bleeding with trauma, and ecchymoses. Typically, these patients are tested using a 1-stage clotting assay. However, new treatment options using long-acting glycoPEGylated replacement products are being approved for clinical use. Pharmacokinetic studies for these products indicate ideal monitoring of patients should be performed by the 2-stage chromogenic assay.

Useful For: Monitoring coagulation factor replacement therapy of selected extended half-life coagulation factor replacements Aiding in the diagnosis of hemophilia B using a 2-stage assay, especially when a 1-stage assay was normal

Interpretation: Factor IX deficiency may be acquired (eg, vitamin K deficiency, warfarin anticoagulation effect, liver disease, or a consumptive coagulopathy) or congenital (hemophilia B). Optimal laboratory monitoring of selected extended half-life factor IX replacement therapy (eg, glycoPEGylated factor FIX) may be achieved with the chromogenic factor IX assay. Elevated factor IX levels may be associated with acute or chronic inflammation, excess factor IX replacement therapy, or rarely, as a result of rare genetic mutation factor IX Padua.

Reference Values:

65-140%

Chromogenic Factor IX activity generally correlates with the one-stage FIX activity. In full term/premature neonates, infants, children, and adolescents the one-stage FIX activity* is similar to adults. However, no similar data for chromogenic FIX activity are available. (Appel JTH 2012; 10:2254)

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.
noacog beta pegol with commercially available one-stage clotting and chromogenic assay kits: a
Signer-Romero K, Key NS: Current laboratory practices in the diagnosis and management of
Ezban M: Factor IX-deficient plasma spiked with N9-GP behaves similarly to N9-GP
post-administration clinical samples in N9-GP ELISA and FIX activity assays. Haemophilia 2015
factor IX for new product labelling and postinfusion testing: challenges for caregivers and regulators.
discrepancies between one-stage clotting and chromogenic assays. Haemophilia 2014
Nov;20(6):891-897

CH8 65028

Chromogenic Factor VIII Activity Assay, Plasma

Clinical Information: Factor VIII (FVIII) is synthesized in the endothelial cells of the liver, and
perhaps in other tissues. It is a coagulation cofactor that circulates bound to von Willebrand factor and is
part of the intrinsic coagulation pathway. The biological half-life is 9 to 18 hours (average is 12 hours).
Congenital FVIII deficiency results in hemophilia A, which has an incidence of 1 in 10,000 live male
births, and is inherited in a recessive X-linked manner. Patients with severe deficiency (<1%)
experience spontaneous bleeding episodes (eg, hemarthrosis, deep-tissue bleeding, etc), whereas
patients with moderate or mild deficiency (>1%) typically experience posttrauma or surgical bleeding.
FVIII activity assays (FVIII:C) are performed to diagnose hemophilia A and to monitor FVIII
replacement therapy. FVIII:C assays are typically 1-stage clotting assays. However, there is a subset of
mild hemophilia A patients who have shown discrepancy low results when measured with the 2-stage
(chromogenic) assay, indicating that testing patients with a mild bleeding history with both a 1- and
2-stage assay would aid in diagnosis. In addition, there are new treatment options using long-acting
glycoPEGylated products. Pharmacokinetic studies are showing that ideal monitoring of patients should
be performed by the 2-stage chromogenic assay.

Useful For: Monitoring coagulation factor replacement therapy of selected extended half-life
coacluation factor replacements Aiding in the diagnosis of hemophilia A using a 2-stage assay,
especially when the 1-stage assay was normal

Interpretation: Factor VIII deficiency may be seen in congenital hemophilia A, acquired
(autoimmune) hemophilia A, or von Willebrand disease (congenital and acquired). Laboratory artifacts
that may result in artificially reduced factor VIII include samples collected in EDTA, instead of citrate,
or heparin contamination of the plasma sample. Elevated factor VIII may be seen in acute or chronic
inflammatory states, or excess factor VIII replacement therapy.

Reference Values:
55-200%

Chromogenic Factor VIII activity generally correlates with the one-stage FVIII activity. In full
term/premature neonates, infants, children, and adolescents the one-stage FVIII activity* is similar to
adults. However, no similar data for chromogenic FVIII activity are available.(Appel JTH
2012;10:2254)

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

Clinical References: 1. Rodgers SE, Duncan EM, Sobieraj-Teague M, Lloyd JV: Evaluation of
three automated chromogenic FVIII kits for the diagnosis of mild discrepant haemophilia A. Int J Lab
recombinant factor VIII: results from an International comparative laboratory field study. Haemophilia
factor IX for new product labelling and postinfusion testing: challenges for caregivers and regulators.
Chromogranin A (CGA) is a 439-amino acid protein with a molecular weight of 48 to 60 kDa, depending on glycosylation and phosphorylation status. It is a member of the granin family of proteins and polypeptides. Granins are widespread in endocrine, neuroendocrine, peripheral, and central nervous tissues, where they are found in secretory granules alongside the tissue-specific secretion products. The role of granins within the granules is to maintain the regulated secretion of these signaling molecules. This includes: -Facilitating the formation of secretory granules -Calcium- and pH-mediated sequestration and resolubilization of hormones or neurotransmitters -Regulation of neuropeptide and peptide hormone processing through modulation of prohormone convertase activity. In addition, granins contain multiple protease and peptidase cleavage sites, and upon intra- or extracellular cleavage give rise to a series of daughter peptides with distinct extracellular functions. Some of these have defined functions, such as pancreastatin, vasostatin, and catestatin, while others are less well characterized.(1) Because of its ubiquitous distribution within neuroendocrine tissues, CGA can be a useful diagnostic marker for neuroendocrine neoplasms, including carcinoids, pheochromocytomas, neuroblastomas, medullary thyroid carcinomas (MTC), some pituitary tumors, functioning and nonfunctioning islet cell tumors, and other amine precursor uptake and decarboxylation (APUD) tumors. It can also serve as a sensitive means for detecting residual or recurrent disease in treated patients.(2-4) Carcinoid tumors in particular almost always secrete CGA along with a variety of specific modified amines, chiefly serotonin (5-hydroxytryptamine: 5-HT) and peptides.(1-4) Carcinoid tumors are subdivided into foregut carcinoids, arising from respiratory tract, stomach, pancreas or duodenum (approximately 15% of cases); midgut carcinoids, occurring within jejunum, ileum, or appendix (approximately 70% of cases); and hindgut carcinoids, which are found in the colon or rectum (approximately 15% of cases). Carcinoids display a spectrum of aggressiveness with no clear distinguishing line between benign and malignant. In advanced tumors, morbidity and mortality relate as much, or more, to the biogenic amines and peptide hormones secreted, as to local and distant spread. The symptoms of this carcinoid syndrome consist of flushing, diarrhea, right-sided valvular heart lesions, and bronchoconstriction. Serum CGA and urine 5-hydroxyindolacetic acid (5-HIAA) are considered the most useful biochemical markers and are first-line tests in disease surveillance of most patients with carcinoid tumors.(2-4) Serum CGA measurements are used in conjunction with, or alternative to, measurements of serum or whole blood serotonin, urine serotonin, and urine 5-HIAA and imaging studies. This includes the differential diagnosis of isolated symptoms suggestive of carcinoid syndrome, in particular flushing. Finally, a number of tumors that are not derived from classical endocrine or neuroendocrine tissues, but contain cells with partial neuroendocrine differentiation, such as small-cell carcinoma of the lung or prostate carcinoma, may also display elevated CGA levels. The role of CGA measurement is not well defined in these tumors, with the possible exception of prognostic information in advanced prostate cancer.(5)

Useful For: Follow-up or surveillance of patients with known or treated carcinoid tumors An adjunct in the diagnosis of carcinoid tumors An adjunct in the diagnosis of other neuroendocrine tumors, including pheochromocytomas, medullary thyroid carcinomas, functioning and nonfunctioning islet cell and gastrointestinal amine precursor uptake and decarboxylation tumors, and pituitary adenomas A possible adjunct in outcome prediction and follow-up in advanced prostate cancer

Interpretation: Follow-up/Surveillance: Urine 5-hydroxyindolacetic acid (5-HIAA) and serum chromogranin A (CGA) increase in proportion to carcinoid tumor burden. Because of the linear relationship of CGA to tumor burden, its measurement also provides prognostic information. Most mid- and hindgut tumors secrete CGA even if they do not produce significant amounts of serotonin or serotonin metabolites (5-HIAA). Guidelines recommend 3 to 12 monthly measurements of CGA or 5-HIAA in follow-up of midgut carcinoids.(2,3) Patients with foregut tumors can also be monitored with CGA or 5-HIAA measurements, if they were positive for these markers at initial diagnosis. Hindgut tumors usually do not secrete serotonin, and consequently only CGA monitoring is recommended.(1-4) As is typical for tumor marker use in follow-up and surveillance, a 40% to 50% change in serum CGA concentrations should be considered potentially clinically significant in the absence of confounding factors (see Cautions). Much smaller changes in CGA concentrations might be considered significant if they occur over several serial measurements and are all in the same direction. Adjunct in Diagnosis of
Carcinoid Tumors: CGA is elevated in most patients (approximately 90%) with symptomatic or advanced carcinoids (carcinoid syndrome), usually to levels several times the upper limit of the reference interval. Serum CGA measurements are particularly suited for diagnosing hindgut tumors, being elevated in nearly all cases, even though serotonin and 5-HIAA are often normal. CGA is also elevated in 80% to 90% of patients with symptomatic foregut and midgut tumors. To achieve maximum sensitivity in the initial diagnosis of suspected carcinoid tumors, serum CGA, serotonin in serum or blood, and 5-HIAA in urine should all be measured. In most cases, if none of these 3 analytes is elevated, carcinoids can usually be excluded as a cause of symptoms suggestive of carcinoid syndrome. For some cases, additional tests such as urine serotonin measurement will be required. An example would be a foregut tumor, which does not secrete CGA and only produces 5-hydroxytryptophan (5-HP), rather than serotonin. In this case, circulating chromogranin, serotonin, and urine 5-HIAA levels would not be elevated. However, the kidneys can convert 5-HP to serotonin, leading to high urine serotonin levels. Adjunct in the Diagnosis of Other Neuroendocrine Tumors: In patients with suspected neuroendocrine tumors other than carcinoids, CGA is often elevated alongside any specific amine and peptide hormones or neurotransmitters that may be produced. The CGA elevations are less pronounced than in carcinoid tumors, and measurement of specific tumor secretion products is considered of greater utility. However, CGA measurements can occasionally aid in diagnosis of these tumors if specific hormone measurements are inconclusive. This is the case in particular with pheochromocytoma and neuroblastoma, where CGA levels may be substantially elevated and can, therefore, provide supplementary and confirmatory information to measurements of specific hormones. In particular, CGA measurements might provide useful diagnostic information in patients with mild elevations in catecholamines and metanephrines; such mild elevations often represent false-positive test results. Possible Adjunct in Outcome Prediction and Follow-up of Prostate Cancer: Prostate cancers often contain cells with partial neuroendocrine differentiation. These cells secrete CGA. The amounts secreted are insufficient in most cases to make this a useful marker for prostate cancer diagnosis. However, if patients with advanced prostate cancer are found to have elevated CGA levels, this indicates the tumor contains a significant neuroendocrine cell subpopulation. Such tumors are often resistant to antiandrogen therapy and have a worse prognosis. These patients should be monitored particularly closely.

Reference Values:

<93 ng/mL

Reference values apply to all ages.

Clinical References:

CHRO 70402 Chromogranin Immunostain, Technical Component Only

Clinical Information: Chromogranin A is widely expressed in neuronal tissues and in secretory granules of human endocrine cells such as parathyroid gland, adrenal medulla, anterior pituitary gland,
Langerhans islets of the pancreas, and C-cells of the thyroid. It is useful for the identification of tumors with neuroendocrine differentiation such as pituitary adenomas, islet cell tumors, pheochromocytomas, medullary thyroid carcinomas, Merkel cell tumors, and carcinoids.

**Useful For:** Aids in the identification of tumors with neuroendocrine differentiation

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**Chromosomal Microarray (CMA) Familial Testing, FISH**

**Clinical Information:** Chromosomal microarray (CMA) is a method for detecting copy number changes (gains or losses) across the entire genome. When copy number changes are identified in a patient, parental studies are sometimes necessary to assess their clinical significance. Changes that are inherited from clinically normal parents are less likely to be clinically significant in the patient and de novo changes are more likely to be pathogenic. To identify familial copy number changes in parents of previously tested patients, FISH testing is utilized. The parental results will provide the context for interpretation of the patient's CMA results.

**Useful For:** Determining the inheritance pattern of copy number changes previously identified by chromosomal microarray analysis in a patient and aiding in the clinical interpretation of the pathogenicity of the copy number change

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Chromosomal Microarray, Autopsy, Products of Conception, or Stillbirth**

**Clinical Information:** Chromosomal abnormalities may result in malformed fetuses, spontaneous abortions, or neonatal deaths. Estimates of the frequency of chromosome abnormalities in spontaneously aborted fetuses range from 15% to 60%. Chromosomal microarray (CMA) studies of products of current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
conception (POC), a stillborn infant, or neonate (autopsy) may provide useful information concerning the cause of fetal loss. In addition, CMA may provide information regarding the recurrence risk for future pregnancy loss and risk of having subsequent children with chromosome anomalies. This is particularly useful information if there is a family history of 2 or more miscarriages or when fetal malformations are evident. CMA is a high-resolution method for detecting copy number changes (gains or losses) across the entire genome in a single assay and is sometimes called a molecular karyotype. This CMA test utilizes more than 1.9 million copy number probes and approximately 750,000 single nucleotide polymorphism probes for the detection of copy number changes and regions with absence of heterozygosity. Identification of regions of excess homozygosity on a single chromosome could suggest uniparental disomy that may warrant further clinical investigation when observed on chromosomes with known imprinting disorders. In addition, the detection of excess homozygosity on multiple chromosomes may suggest consanguinity.

**Useful For:** Prenatal diagnosis of copy number changes (gains or losses) across the entire genome
Diagnosing chromosomal causes for fetal death
Determining recurrence risk of future pregnancy losses
Determining the size, precise breakpoints, gene content, and any unappreciated complexity of abnormalities detected by other methods such as conventional chromosome and FISH studies
Determining if apparently balanced abnormalities identified by previous conventional chromosome studies have cryptic imbalances, since a proportion of such rearrangements that appear balanced at the resolution of a chromosome study are actually unbalanced when analyzed by higher-resolution chromosomal microarray
Assessing regions of homozygosity related to uniparental disomy or identical by descent

**Interpretation:** Copy number variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. While many copy number changes observed by chromosomal microarray testing can readily be characterized as pathogenic or benign, there are limited data available to support definitive classification of a subset into either of these categories, making interpretation of these variants challenging. In these situations, a number of considerations are taken into account to help interpret results including the size and gene content of the imbalance, as well as whether the change is a deletion or duplication. Parental testing may also be necessary to further assess the potential pathogenicity of a copy number change. In such situations, the inheritance pattern and clinical and developmental history of the transmitting parent will be taken into consideration. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding. The detection of excess homozygosity may suggest the need for additional clinical testing to confirm uniparental disomy or to test for mutations in genes associated with autosomal recessive disorders present in regions of homozygosity.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

CMAMT 62667 Chromosomal Microarray, Autopsy/Products of Conception/Stillbirth, Tissue

**Clinical Information:** Chromosomal abnormalities may result in malformed fetuses, spontaneous abortions, or neonatal deaths. Estimates of the frequency of chromosome abnormalities in spontaneously aborted fetuses range from 15% to 60%. Chromosomal microarray (CMA) studies of products of conception (POC), a stillborn infant, or a neonate (autopsy) may provide useful information concerning the cause of fetal loss. In addition, CMA may provide information regarding the recurrence risk for future pregnancy loss and risk of having subsequent children with chromosome anomalies. This is particularly useful information if there is a family history of 2 or more miscarriages or when fetal malformations are evident. CMA is a high-resolution method for detecting copy number changes (gains or losses) across the entire genome in a single assay and is sometimes called a molecular karyotype. This CMA test utilizes more than 1.9 million copy number probes and approximately 750,000 single nucleotide polymorphism probes for the detection of copy number changes and regions with absence of heterozygosity. Identification of regions of excess homozygosity on a single chromosome could suggest uniparental disomy that may warrant further clinical investigation when observed on chromosomes with known imprinting disorders. In addition, the detection of excess homozygosity on multiple chromosomes may suggest consanguinity.

**Useful For:** Prenatal diagnosis of copy number changes (gains or losses) across the entire genome
Diagnosing chromosomal causes for fetal death
Determining recurrence risk of future pregnancy losses
Determining the size, precise breakpoints, gene content, and any unappreciated complexity of abnormalities detected by other methods such as conventional chromosome and FISH studies
Determining if apparently balanced abnormalities identified by previous conventional chromosome studies have cryptic imbalances, since a proportion of such rearrangements that appear balanced at the resolution of a chromosome study are actually unbalanced when analyzed by higher-resolution chromosomal microarray
Assessing regions of homozygosity related to uniparental disomy or identical by descent

**Interpretation:** Copy number variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. While many copy number changes observed by chromosomal microarray testing can readily be characterized as pathogenic or benign, there are limited data available to support definitive classification of a subset into either of these categories, making interpretation of these variants challenging. In these situations, a number of considerations are taken into account to help interpret results including the size and gene content of the imbalance, as well as whether the change is a deletion or duplication. Parental testing may also be necessary to further assess the potential pathogenicity of a copy number change. In such situations, the inheritance pattern and clinical and developmental history of the transmitting parent will be taken into consideration. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding. The detection of excess homozygosity may suggest the need for additional clinical testing to confirm uniparental disomy or to test for mutations in genes associated with autosomal recessive disorders present in regions of homozygosity.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
concerning the cause of miscarriage or fetal loss. In addition, CMA may provide information regarding
the recurrence risk for future pregnancy loss and risk of having subsequent children with chromosome
anomalies. This is particularly useful information if there is a family history of 2 or more miscarriages
or when fetal malformations are evident. CMA is a high-resolution method for detecting copy number
changes (gains or losses) across the entire genome in a single assay and is sometimes called a molecular
karyotype. This CMA test utilizes over 220,000 markers for the detection of copy number changes and
regions with absence of heterozygosity. Identification of regions of excess homozygosity on a single
chromosome could suggest uniparental disomy that may warrant further clinical investigation when
observed on chromosomes with known imprinting disorders. In addition, the detection of excess
homozygosity on multiple chromosomes may suggest consanguinity.

Useful For: Diagnosis of congenital copy number changes in products of conception, including
aneuploidy (ie, trisomy or monosomy) and structural abnormalities. Diagnosing chromosomal causes for
fetal death. Determining recurrence risk of future pregnancy losses. Determining the size, precise
breakpoints, gene content, and any unappreciated complexity of abnormalities detected previously by
other methods such as conventional chromosome and FISH studies. Determining if apparently balanced
abnormalities identified by previous conventional chromosome studies have cryptic imbalances, since a
proportion of such rearrangements that appear balanced at the resolution of a chromosome study are
actually unbalanced when analyzed by higher-resolution chromosomal microarray

Interpretation: Copy number variants are classified based on known, predicted, or possible
pathogenicity and reported with interpretive comments detailing their potential or known significance. A
normal result will be reported as arr(1-22,X)x2 or arr(1-22)x2,(XY)x1. A copy number change known to
be of clinical significance will be reported as pathogenic. Copy number changes with unknown
significance will be reported as either likely benign, uncertain, or likely pathogenic. Absence of
heterozygosity will be reported. While many copy number changes observed by chromosomal microarray
testing can readily be characterized as pathogenic or benign, there are limited data available to support
definitive classification of a subset into either of these categories, making interpretation of these variants
challenging. In these situations, a number of considerations are taken into account to help interpret results
including the size and gene content of the imbalance, as well as whether the change is a deletion or
duplication. Parental testing may also be necessary to further assess the potential pathogenicity of a copy
number change. In such situations, the inheritance pattern and clinical and developmental history of the
transmitting parent will be taken into consideration. The continual discovery of novel copy number
variation and published clinical reports means that the interpretation of any given copy number change
may evolve with increased scientific understanding. The detection of excess homozygosity may suggest
the need for additional clinical testing to confirm uniparental disomy or to test for mutations in genes
associated with autosomal recessive disorders present in regions of homozygosity.

Reference Values:
An interpretive report will be provided.

Clinical References: 1. American College of Obstetricians and Gynecologists Committee on
Genetics: Committee opinion No. 581: the use of chromosomal microarray analysis in prenatal diagnosis.
counseling of couples with recurrent miscarriage: recommendations of the National Society of Genetic

Chromosomal Microarray, Congenital, Blood

Clinical Information: Aneuploidy or unbalanced chromosome rearrangements are often found in
patients with intellectual disability, developmental delay, autism, dysmorphic features, or congenital
anomalies. Some chromosomal abnormalities are large enough to be detected with conventional
chromosome analysis. However, many pathogenic rearrangements are below the resolution limits of
chromosome analysis (approximately 5 megabases). Chromosomal microarray (CMA) is a high-resolution
method for detecting copy number changes (gains or losses) across the entire genome in a single assay and is sometimes called a molecular karyotype. This CMA test utilizes greater than 1.9 million copy number probes and approximately 750,000 single nucleotide polymorphism probes for the detection of copy number changes and regions of excessive homozygosity. Identification of regions of excessive homozygosity on a single chromosome could suggest uniparental disomy (UPD), which may warrant further clinical investigation when observed on chromosomes with known imprinting disorders associated with UPD. In addition, the detection of excessive homozygosity on multiple chromosomes may suggest consanguinity and, therefore, could be useful in determining candidate genes for further testing for autosomal recessive disorders. As a participant in the International Standard Cytogenomic Array Consortium (ISCA) (see Chromosomal Microarray Testing and the ISCA Consortium Database in Special Instructions), Mayo Clinic Cytogenetics Laboratory contributes submitted clinical information and test results for molecular cytogenetic tests to a HIPAA-compliant, deidentified public database hosted by the National Institute of Health. This is an international effort to improve diagnostic testing and our understanding of the relationships between genetic changes and clinical symptoms (for information about the database visit the consortium website at https://www.iscaconsortium.org). Confidentiality of each specimen is maintained. Patients may request to opt-out of this scientific effort by calling the laboratory at 800-533-1710, extension 4-1668, and asking to speak with a laboratory genetic counselor. Please call with any questions. An online research opportunity called GenomeConnect (genomeconnect.org) is available for the recipients of genetic test results. This patient registry collects deidentified genetic and health information to advance knowledge of genetic variants. See GenomeConnect Patient Portal in Special Instructions for more information.

**Useful For:** First-tier, postnatal testing for individuals with multiple anomalies that are not specific to well-delineated genetic syndromes, apparently nonsyndromic developmental delay or intellectual disability, or autism spectrum disorders as recommended by the American College of Medical Genetics (ACMG) Follow-up testing for individuals with unexplained developmental delay or intellectual disability, autism spectrum disorders, or congenital anomalies with a previously normal conventional chromosome study Determining the size, precise breakpoints, gene content, and any unappreciated complexity of abnormalities detected by other methods such as conventional chromosome and FISH studies Determining if apparently balanced abnormalities identified by previous conventional chromosome studies have cryptic imbalances, since a proportion of such rearrangements that appear balanced at the resolution of a chromosome study are actually unbalanced when analyzed by higher-resolution chromosomal microarray Assessing regions of homozygosity related to uniparental disomy or identity by descent

**Interpretation:** When interpreting results, the following factors need to be considered: Copy number variation is found in all individuals, including patients with abnormal phenotypes and normal populations. Therefore, determining the clinical significance of a rare or novel copy number change can be challenging. Parental testing may be necessary to further assess the potential pathogenicity of a copy number change. While most copy number changes observed by chromosomal microarray testing can readily be characterized as pathogenic or benign, there are limited data available to support definitive classification of a subset into either of these categories. In these situations, a number of considerations are taken into account to help interpret results including the size and gene content of the imbalance, whether the change is a deletion or duplication, the inheritance pattern, and the clinical and/or developmental history of a transmitting parent. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding. The detection of excessive homozygosity may suggest the need for additional clinical testing to confirm uniparental disomy or to test for mutations in genes associated with autosomal recessive disorders consistent with the patient's clinical presentation that are present in regions of homozygosity. Families benefit from hearing genetic information multiple times and in multiple ways. A referral to a clinical genetics professional is appropriate for individuals and families to discuss the results of chromosomal microarray testing.

**Reference Values:**
An interpretive report will be provided.

et al: Consensus statement: Chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet 2010;86:749-764

CMAH 35899

Chromosomal Microarray, Hematologic Disorders

Clinical Information: The importance of identifying chromosome abnormalities in hematologic disorders is well established, and often provides important diagnostic, prognostic, and therapeutic information critical to proper patient management. Although many chromosomal abnormalities are large enough to be detected with conventional chromosome analysis, many others are below its limits of resolution, and conventional chromosome analysis does not detect copy-neutral loss of heterozygosity. Chromosomal microarray (CMA) improves the diagnostic yield to identify genetic changes that are not detected by conventional chromosome analysis or FISH studies. CMA utilizes >1.9 million copy number probes and approximately 750,000 single nucleotide polymorphism probes to detect copy number changes and regions of copy-neutral loss of heterozygosity. CMA analysis is appropriate to identify gain or loss of chromosome material throughout the genome at a resolution of 30 to 60 kilobases. CMA can do the following: -Define the size, precise breakpoints, and gene content of copy number changes to demonstrate the complexity of abnormalities -Characterize unidentified chromosome material, marker chromosomes, and DNA amplification detected by conventional chromosome and FISH studies  -Determine if apparently balanced chromosome rearrangements identified by conventional chromosome studies have cryptic imbalances -Assess regions of copy-neutral loss of heterozygosity, which is common in neoplasia and often masks homozygous mutations involving tumor suppressor genes The limit of detection is dependent on size of the abnormality, type of abnormality (deletion or duplication) and DNA quality. When a deletion or duplication exceeds the reporting limits, mosaicism can confidently be detected as low as 25% and may be lower if the abnormality is large and DNA quality is good.

Useful For: Detection and characterization of clonal copy number imbalance and loss of heterozygosity associated with hematologic neoplasms Assisting in the diagnosis and classification of certain hematologic neoplasms Evaluating the prognosis for patients with certain hematologic neoplasms

Interpretation: The interpretive report describes copy number changes and any loss of heterozygosity that may be associated with the neoplastic process. Abnormal clones with subclonal cytogenetic evolution will be discussed if identified. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding. Although the presence of a clonal abnormality usually indicates a neoplasia, in some situations it may reflect a benign or constitutional genetic change. If a genetic change is identified that is likely constitutional and clearly pathogenic (eg, XYY), follow-up with a medical genetics consultation may be suggested. The absence of an abnormal clone may be the result of specimen collection from a site that is not involved in the neoplasm, or may indicate that the disorder is caused by a point mutation that is not detectable by chromosomal microarray (CMA). CMA, FISH, and conventional cytogenetics are to some extent complementary methods. In some instances, additional FISH or conventional cytogenetic studies will be recommended to clarify interpretive uncertainties.

Reference Values:
An interpretive report will be provided.

Chromosomal Microarray, Prenatal, Amniotic Fluid/Chorionic Villus Sampling

Clinical Information: Chromosomal abnormalities cause a wide range of disorders associated with birth defects and intellectual disability. Many of these disorders can be diagnosed prenatally by analysis of chorionic villi or amniocytes. The most common reasons for performing cytogenetic studies for prenatal diagnosis include advanced maternal age, abnormal prenatal screen, a previous child with a chromosome abnormality, abnormal fetal ultrasound, or a family history of a chromosome abnormality. Chromosomal microarray (CMA) is a high-resolution method for detecting copy number changes (gains or losses) across the entire genome in a single assay and is sometimes called a molecular karyotype. The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommend the chromosomal microarray as a replacement for the fetal karyotype in patients with a pregnancy demonstrating one or more major structural abnormalities on ultrasound when undergoing invasive prenatal diagnosis.(1) This CMA test utilizes more than 1.9 million copy number probes and approximately 750,000 single nucleotide polymorphism probes for the detection of copy number changes and regions with absence of heterozygosity. Identification of regions of excessive homozygosity on a single chromosome could suggest uniparental disomy, which may warrant further clinical investigation when observed on chromosomes with known imprinting disorders. In addition, the detection of excessive homozygosity on multiple chromosomes may suggest consanguinity.

Useful For: Prenatal diagnosis of copy number changes (gains or losses) across the entire genome Determining the size, precise breakpoints, gene content, and any unappreciated complexity of abnormalities detected by other methods such as conventional chromosome and FISH studies Determining if apparently balanced abnormalities identified by previous conventional chromosome studies have cryptic imbalances, since a proportion of such rearrangements that appear balanced at the resolution of a chromosome study are actually unbalanced when analyzed by higher-resolution chromosomal microarray Assessing regions of homozygosity related to uniparental disomy or identity by descent

Interpretation: Copy number variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. When interpreting results it is important to realize that copy number variation is found in all individuals, including patients with abnormal phenotypes and normal populations. Therefore, determining the clinical significance of a rare or novel copy number change can be challenging. Parental testing may be necessary to further assess the potential pathogenicity of a copy number change. While most copy number changes observed by chromosomal microarray testing can readily be characterized as pathogenic or benign, there are limited data available to support definitive classification of a subset into either of these categories. In these situations, a number of considerations are taken into account to help interpret results including the size and gene content of the imbalance, whether the change is a deletion or duplication, the inheritance pattern, and the clinical and developmental history of a transmitting parent. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding. Copy number changes with unknown significance will be reported when at least 1 gene is involved in a deletion greater than 1 megabase (Mb) or a duplication greater than 2 Mb. The detection of excessive homozygosity may suggest the need for additional clinical testing to confirm uniparental disomy or to test for mutations in genes associated with autosomal recessive disorders consistent with the patient’s clinical presentation that are present in regions of homozygosity. Regions with absence of heterozygosity (AOH) with unknown significance will be reported when greater than 5 Mb (terminal) and 10 Mb (interstitial) on UPD-associated chromosomes. Whole genome AOH will be reported when greater than 10% of the genome.

Reference Values: An interpretive report will be provided.

Clinical References: 1. American College of Obstetricians and Gynecologists Committee on

Chromosomal Microarray, Tumor, Formalin-Fixed Paraffin-Embedded

Clinical Information: The importance of identifying chromosome abnormalities in malignant neoplasms is well established, and often provides important diagnostic, prognostic, and therapeutic information critical to proper patient management. Although many chromosomal abnormalities are large enough to be detected with conventional chromosome analysis, many others are below its limits of resolution, and conventional chromosome analysis does not detect copy-neutral loss of heterozygosity. Chromosomal microarray (CMA) improves the diagnostic yield to identify genetic changes that are not detected by conventional chromosome analysis or FISH studies. CMA utilizes copy number probes and single nucleotide polymorphism probes to detect copy number changes and regions of copy-neutral loss of heterozygosity. CMA analysis is appropriate to identify gain or loss of chromosome material throughout the genome at a resolution of 50 to 100 kilobases. CMA can: -Define the size, precise breakpoints, and gene content of copy number changes to demonstrate the complexity of abnormalities -Characterize unidentified chromosome material, marker chromosomes, and DNA amplification detected by conventional chromosome and FISH studies -Determine if apparently balanced chromosome rearrangements identified by conventional chromosome studies have cryptic imbalances -Assess regions of copy-neutral loss of heterozygosity, which is common in neoplasia and often masks homozygous mutations involving tumor suppressor genes The limit of detection is dependent on size of the abnormality, type of abnormality (deletion or duplication) and DNA quality. When a deletion or duplication exceeds the reporting limits, mosaicism can confidently be detected as low as 25% and may be lower if the abnormality is large and DNA quality is good.

Useful For: Genomic characterization of tumor for copy number imbalances and loss of heterozygosity Assisting in the diagnosis and classification of malignant neoplasms Evaluating the prognosis for patients with malignant tumors

Interpretation: The interpretive report describes copy number changes and any loss of heterozygosity that may be associated with the neoplastic process. Abnormal clones with subclonal cytogenetic evolution will be discussed if identified. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding. Although the presence of a clonal abnormality usually indicates a neoplasia, in some situations it may reflect a benign or constitutional genetic change. If a genetic change is identified that is likely constitutional and clearly pathogenic (eg, XYY), follow-up with a medical genetics consultation may be suggested. The absence of an abnormal clone may be the result of specimen collection from a site that is not involved in the neoplasm, or may indicate that the disorder is caused by a point mutation that is not detectable by chromosomal microarray (CMA). CMA, FISH, and conventional cytogenetics are to some extent complementary methods. In some instances, additional FISH or conventional cytogenetic studies will be recommended to clarify interpretive uncertainties. See Cytogenetic Analysis of Glioma in Special Instructions for common questions and answers.

Reference Values:
An interpretive report will be provided.

**Chromosomal Microarray, Tumor, Fresh or Frozen using Affymetrix Cytoscan HD**

**Clinical Information:** The importance of identifying chromosome abnormalities in malignant neoplasms is well established, and often provides important diagnostic, prognostic, and therapeutic information critical to proper patient management. Although many chromosomal abnormalities are large enough to be detected with conventional chromosome analysis, many others are below its limits of resolution, and conventional chromosome analysis does not detect copy-neutral loss of heterozygosity. Chromosomal microarray (CMA) improves the diagnostic yield to identify genetic changes that are not detected by conventional chromosome analysis or FISH studies. CMA utilizes >1.9 million copy number probes and approximately 750,000 single nucleotide polymorphism probes to detect copy number changes and regions of copy-neutral loss of heterozygosity. CMA analysis is appropriate to identify gain or loss of chromosome material throughout the genome at a resolution of 30 to 60 kilobases. CMA can:

- Define the size, precise breakpoints, and gene content of copy number changes to demonstrate the complexity of abnormalities.
- Characterize unidentified chromosome material, marker chromosomes, and DNA amplification detected by conventional chromosome and FISH studies.
- Determine if apparently balanced chromosome rearrangements identified by conventional chromosome studies have cryptic imbalances.
- Assess regions of copy-neutral loss of heterozygosity, which is common in neoplasia and often masks homozygous mutations involving tumor suppressor genes. The limit of detection is dependent on size of the abnormality, type of abnormality (deletion or duplication) and DNA quality. When a deletion or duplication exceeds the reporting limits, mosaicism can confidently be detected as low as 25% and may be lower if the abnormality is large and DNA quality is good.

**Useful For:** Genomic characterization of tumor for copy number imbalances and loss of heterozygosity. Assisting in the diagnosis and classification of malignant neoplasms, including hematolymphoid malignancies. Evaluating the prognosis for patients with malignant tumors.

**Interpretation:** The interpretive report describes copy number changes and any loss of heterozygosity that may be associated with the neoplastic process. Abnormal clones with subclonal cytogenetic evolution will be discussed if identified. The continual discovery of novel copy number variation and published clinical reports means that the interpretation of any given copy number change may evolve with increased scientific understanding. Although the presence of a clonal abnormality usually indicates a neoplasia, in some situations it may reflect a benign or constitutional genetic change. If a genetic change is identified that is likely constitutional and clearly pathogenic (eg, XYY), follow-up with a medical genetics consultation may be suggested. The absence of an abnormal clone may be the result of specimen collection from a site that is not involved in the neoplasm, or may indicate that the disorder is caused by a point mutation that is not detectable by chromosomal microarray (CMA). CMA, FISH, and conventional cytogenetics are to some extent complementary methods. In some instances, additional FISH or conventional cytogenetic studies will be recommended to clarify interpretive uncertainties.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Clinical Information: Chromosome analysis for prenatal diagnosis is appropriate in pregnancies with abnormal maternal screening, advanced maternal age, and features suggestive of or concerns for aneuploidy syndromes, including Down syndrome, Turner syndrome, Klinefelter syndrome, trisomy 13 syndrome, and trisomy 18 syndrome. Chromosomal abnormalities are the cause of a wide range of disorders associated with birth defects and congenital diseases. Many of these disorders can be diagnosed prenatally by analysis of amniocytes. This method permits diagnosis of chromosome abnormalities during the second trimester of pregnancy or later. A chromosomal microarray (CMAP / Chromosomal Microarray, Prenatal, Amniotic Fluid/Chorionic Villus Sampling) is recommended, rather than chromosomal analysis, to detect clinically relevant gains or losses of chromosomal material in pregnancies with 1 or more major structural abnormalities. Chromosomal microarray can also be considered, rather than chromosome analysis, for patients undergoing invasive prenatal diagnostic testing with a structurally normal fetus.

Useful For: Prenatal diagnosis of chromosome abnormalities, including aneuploidy (ie, trisomy or monosomy) and balanced rearrangements

Interpretation: Cytogenetic studies on amniotic fluid are considered nearly 100% accurate for the detection of large fetal chromosome abnormalities. However, subtle or cryptic abnormalities involving microdeletions usually can be detected only with the use of targeted FISH testing. Approximately 3% of amniotic fluid specimens analyzed are found to have chromosome abnormalities. Some of these chromosome abnormalities are balanced and may not be associated with birth defects. A normal karyotype does not rule out the possibility of birth defects, such as those caused by submicroscopic cytogenetic abnormalities, molecular mutations, and other environmental factors (ie, teratogen exposure). For these reasons, clinicians should inform their patients of the technical limitations of chromosome analysis prior to performing the amniocentesis. It is recommended that a qualified professional in Medical Genetics communicate all results to the patient.

Reference Values:
An interpretative report will be provided.

Clinical References:

CHRPC 35315

Chromosome Analysis, Autopsy, Products of Conception, or Stillbirth

Clinical Information: Chromosome analysis of products of conception, spontaneous abortions, stillborn infants, or neonates is appropriate when previous losses have occurred and features suggestive of or concerns for aneuploidy syndromes, including Down syndrome, Turner syndrome, Klinefelter syndrome, trisomy 13 syndrome and trisomy 18 syndrome. Chromosomal abnormalities may result in malformed fetuses, spontaneous abortions, or neonatal deaths. Estimates of the frequency of chromosome abnormalities in spontaneous abortuses range from 15% to 60%. Chromosome studies of products of conception (POC) may provide useful information concerning the cause of miscarriage and, thus, the recurrence risk for pregnancy loss and risk for having subsequent children with chromosome anomalies. Chromosome analysis of the stillborn infant or neonate (autopsy) may be desirable, particularly if there is a family history of 2 or more miscarriages or when malformations are evident. For neonatal cases, peripheral blood is the preferred specimen for chromosome analysis (CHRCB / Chromosome Analysis, Congenital Disorders, Blood). Some of the chromosome abnormalities that are detected in these specimens are balanced (no apparent gain or loss of genetic material) and may not be associated with birth defects, miscarriage, or stillbirth. For balanced chromosome rearrangements, it is sometimes difficult to determine whether the chromosome abnormality is the direct cause of a miscarriage or stillbirth. In these
situations, chromosome studies of the parents' peripheral blood may be useful to determine if an
abnormality is familial or de novo. De novo, balanced rearrangements can cause miscarriages or stillbirth
by producing submicroscopic deletions, duplications, or gene mutations at the site of chromosome
breakage. A normal karyotype does not rule out the possibility of birth defects, such as those caused by
submicroscopic cytogenetic abnormalities, molecular mutations, and environmental factors (ie, teratogen
exposure). -Subtle structural chromosomal abnormalities can occasionally be missed -Culturing of
maternal cells rather than fetal cells -Chromosome mosaicism may be missed due to statistical sampling
error (rare) A chromosomal microarray (CMAP / Chromosomal Microarray, Prenatal, Amniotic
Fluid/Chorionic Villus Sampling) is recommended, rather than chromosomal analysis, to detect clinically
relevant gains or losses of chromosomal material in instances of intrauterine fetal demise or stillbirth.

**Useful For:** Diagnosis of congenital chromosome abnormalities in products of conception, including
aneuploidy (ie, trisomy or monosomy)

**Interpretation:** A normal result is a karyotype of 46,XX or 46,XY. A chromosome abnormality
known to be pathogenic will be reported as abnormal. Apparently balanced rearrangements will be
reported. On rare occasions, structural changes with unknown clinical significance will be identified and
reported. Due to bacterial contamination or nonviable cells, we are unable to establish a viable culture
20% of the time. In these cases, the specimen cannot be used for chromosome analysis, and the FISH
aneuploidy test (POCRF / Products of Conception (POC) Aneuploidy Detection, FISH, Fresh Tissue) is
automatically initiated. While the FISH test is not as comprehensive as a chromosome analysis, it can
provide information with regard to the most common numeric abnormalities in spontaneous miscarriage
and stillbirth. A FISH signal pattern with 2 signals for 13, 15, 16, 18, 21, 22 and either 2 signals for
chromosome X or one signal for chromosome X and one signal for chromosome Y in each interphase
will be reported as normal. A FISH signal pattern indicating an additional signal (3 signals) in each
interphase will be reported as having a trisomy of the chromosome identified. A FISH signal pattern
indicating loss of a signal (1 signal) will be reported as having a monosomy of the chromosome
identified. A FISH signal pattern indicating an additional signal for every chromosome (3 signals for X
and/or Y and 3 signals for chromosomes 13, 15, 16, 18, 21, 22) will be reported as having triploidy.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
1. Laurino MY, Bennett RL, Saraiya DS, et al: Genetic evaluation and
counseling of couples with recurrent miscarriage: recommendations of the National Society of Genetic
Committee on Genetics: Committee Opinion No. 581: the use of chromosomal microarray analysis in
2016;215:B2-B9

**CHRBF**

**Chromosome Analysis, Body Fluid**

**Clinical Information:** Cytogenetic studies on body fluids (eg, pleural effusions, ascites, and
pericardial, cerebrospinal, and synovial fluids) may be helpful to diagnose or to rule-out metastases or
relapses in patients with lymphoma or other malignancies. Chromosome analysis serves as a useful
adjunct to cytology. In pleural fluids, lymphomas are often more readily diagnosed by cytogenetic
techniques than by standard cytologic examination.

**Useful For:** Assisting in the diagnosis of certain malignancies

**Interpretation:** The observation of a chromosomally abnormal clone is evidence of a clonal
neoplastic process. A normal karyotype does not eliminate the possibility of a neoplastic process. On
rare occasions, the presence of an abnormality may be associated with a congenital abnormality that is
not related to a malignant neoplastic process. Follow-up with a medical genetics consultation is
recommended.

**Reference Values:**
An interpretive report will be provided.

CHRCV 35251

Chromosome Analysis, Chorionic Villus Sampling

Clinical Information: Although not used as widely as amniocentesis, the use of chorionic villus sampling (CVS) for chromosome analysis is an important procedure for the prenatal diagnosis of chromosome abnormalities. CVS can be collected by either transcervical or transabdominal techniques. The medical indications for performing chromosome studies on CVS are similar to amniocentesis, and may include advanced maternal age, abnormal first-trimester screen, and family history of a chromosome abnormality. A chromosomal microarray (CMAP / Chromosomal Microarray, Prenatal) is recommended, rather than chromosomal analysis, to detect clinically relevant gains or losses of chromosomal material in pregnancies with one or more major structural abnormalities. Chromosomal microarray can also be considered, rather than chromosome analysis, for patients undergoing invasive prenatal diagnostic testing with a structurally normal fetus.

Useful For: Prenatal diagnosis of chromosome abnormalities, including aneuploidy (ie, trisomy or monosomy) and balanced rearrangements This test is not appropriate as a first-tier test for detecting gains or losses of chromosomal material in pregnancies with 1 or more major structural abnormalities.

Interpretation: Cytogenetic studies on chorionic villus specimen (CVS) are considered more than 99% reliable for the detection of most fetal chromosome abnormalities. However, subtle or cryptic abnormalities involving microdeletions usually can be detected only with the use of targeted FISH testing. Approximately 3% of CSVs analyzed are found to have chromosome abnormalities. Some of these chromosome abnormalities are balanced and may not be associated with birth defects. A normal karyotype does not rule out the possibility of birth defects, such as those caused by submicroscopic cytogenetic abnormalities, molecular mutations, and environmental factors (ie, teratogen exposure). For these reasons, clinicians should inform their patients of the technical limitations of chromosome analysis before the procedure is performed, so that patients may make an informed decision about pursuing the procedure. Limitations: -False-chromosome mosaicism may occur due to artifact of culture -True mosaicism may be missed due to statistical sampling error -Presence of chromosome abnormalities in placental cells that do not occur in the cells of the fetus (confined placental mosaicism) -Subtle structural chromosome abnormalities can occasionally be missed It is recommended that a qualified professional in Medical Genetics communicate all results to the patient.

Reference Values: An interpretive report will be provided.


CHRCB 35248

Chromosome Analysis, Congenital Disorders, Blood

Clinical Information: Chromosome analysis is appropriate for individuals with clinical features including infertility, multiple miscarriages, delayed puberty, ambiguous genitalia, amenorrhea, or individuals with clinical features suggestive of an aneuploidy syndrome, including Down syndrome, Turner syndrome, Klinefelter syndrome, Trisomy 13 syndrome, and Trisomy 18 syndrome. A chromosomal microarray study (CMACB / Chromosomal Microarray, Congenital, Blood) is recommended as the first-tier test (rather than a congenital chromosome study) to detect clinically
relevant gains or losses of chromosomal material for individuals with multiple anomalies not specific to well-delineated genetic syndromes, individuals with apparently nonsyndromic developmental delay or intellectual disability, and individuals with autism spectrum disorders. Chromosome analysis may be appropriate for this patient population if microarray has been performed with normal results. Some chromosome rearrangements are balanced (no gain or loss of material) and, therefore, not detectable by chromosomal microarray. In rare situations these rearrangements may interrupt gene functioning and have the potential to cause abnormal clinical features. Limitations: A normal karyotype (46,XX or 46,XY with no apparent chromosome abnormality) does not eliminate the possibility of abnormal clinical features such as those caused by submicroscopic cytogenetic abnormalities, molecular mutations, and environmental factors (ie, teratogen exposure). Chromosomal mosaicism may be missed due to statistical sampling error (rare) and subtle structural chromosome abnormalities can occasionally be missed.

**Useful For:** Diagnosis of congenital chromosome abnormalities, including aneuploidy, structural abnormalities, and balanced rearrangements

**Interpretation:** When interpreting results, the following factors need to be considered: -Some chromosome abnormalities are balanced (no apparent gain or loss of genetic material) and may not be associated with birth defects. However, balanced abnormalities often cause infertility and, when inherited in an unbalanced fashion, may result in birth defects in the offspring. -A normal karyotype (46,XX or 46,XY with no apparent chromosome abnormality) does not eliminate the possibility of birth defects such as those caused by submicroscopic cytogenetic abnormalities, molecular mutations, and environmental factors (ie, teratogen exposure). It is recommended that a qualified professional in Medical Genetics communicate all abnormal results to the patient.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Chromosome Analysis, Congenital Disorders, Fixed Cells**

**Clinical Information:** Chromosome analysis is appropriate for individuals with clinical features including infertility, multiple miscarriages, delayed puberty, ambiguous genitalia, amenorrhea, or individuals with clinical features suggestive of an aneuploidy syndrome, including Down syndrome, Turner syndrome, Klinefelter syndrome, trisomy 13 syndrome, and trisomy 18 syndrome. A chromosomal microarray study (CMACB / Chromosomal Microarray, Congenital, Blood) is recommended as the first-tier test (rather than a congenital chromosome study) to detect clinically relevant gains or losses of chromosomal material for individuals with multiple anomalies not specific to well-delineated genetic syndromes, individuals with apparently nonsyndromic developmental delay or intellectual disability, and individuals with autism spectrum disorders. Chromosome analysis may be appropriate for this patient population if microarray has been performed with normal results. Some chromosome rearrangements are balanced (no gain or loss of material) and therefore not detectable by chromosomal microarray. In rare situations, these rearrangements may interrupt gene functioning and have the potential to cause abnormal clinical features. Limitations: A normal karyotype (46,XX or 46,XY with no apparent chromosome abnormality) does not eliminate the possibility of abnormal clinical features such as those caused by submicroscopic cytogenetic abnormalities, molecular mutations, and environmental factors (ie, teratogen exposure). Chromosomal mosaicism may be missed due to statistical sampling error (rare) and subtle structural chromosome abnormalities can occasionally be missed.

**Useful For:** Diagnosis of congenital chromosome abnormalities, including aneuploidy, structural
Interpretation: When interpreting results, the following factors need to be considered: -Some chromosome abnormalities are balanced (no apparent gain or loss of genetic material) and may not be associated with birth defects. However, balanced abnormalities often cause infertility and, when inherited in an unbalanced fashion, may result in birth defects in the offspring. -A normal karyotype (46,XX or 46,XY with no apparent chromosome abnormality) does not eliminate the possibility of birth defects such as those caused by submicroscopic cytogenetic abnormalities, molecular mutations, and environmental factors (ie, teratogen exposure). -Chromosomal mosaicism may be missed due to statistical sampling error (rare) -Subtle structural chromosome abnormalities can occasionally be missed -It is recommended that a qualified professional in Medical Genetics communicate all abnormal results to the patient.

Reference Values:
An interpretive report will be provided.

Clinical References:

Chromosome Analysis, Hematologic Disorders, Blood

Clinical Information: Chromosomal abnormalities play a central role in the pathogenesis, diagnosis, and monitoring of treatment of many hematologic disorders. Whenever possible, it is best to do chromosome studies for neoplastic hematologic disorders on bone marrow. Bone marrow studies are more sensitive and the chances of finding metaphases are about 95%, compared with only a 60% chance for blood studies. When it is not possible to collect bone marrow, chromosome studies on blood may be useful. When blood cells are cultured in a medium without mitogens, the observation of any chromosomally abnormal clone may be consistent with a neoplastic process. See Laboratory Screening Tests for Suspected Multiple Myeloma in Special Instructions. Conventional chromosome studies of B-cell disorders are not always successful because B-lymphocytes do not proliferate well in cell culture. The agent CpG 7909 (CpG) is a synthetic oligodeoxynucleotide that binds to the Toll-like receptor 9 (TLR9) present on B cells, causing B-cell activation. In the laboratory setting, CpG may be used as a mitogen to stimulate B-cells in patient specimens, thus allowing identification of chromosome abnormalities. CpG stimulation reveals an abnormal karyotype in approximately 80% of patients with chronic lymphocytic leukemia (CLL), and the karyotype is complex in 20% to 25% of cases. Several studies have reported that increased genetic complexity revealed by CpG-stimulated chromosome studies confers a less favorable time to first treatment, treatment response, and overall survival.

Useful For: Assisting in the classification and follow-up of certain malignant hematological disorders when bone marrow is not available

Interpretation: The presence of an abnormal clone usually indicates a malignant neoplastic process. The absence of an apparent abnormal clone in blood may result from a lack of circulating abnormal cells and not from an absence of disease. On rare occasions, the presence of an abnormality may be associated with a congenital abnormality and, thus, not related to a malignant process. When this situation is suspected, follow-up with a medical genetics consultation is recommended.

Reference Values:
An interpretative report will be provided.

Chromosome Analysis, Hematologic Disorders, Bone Marrow

Clinical Information: Chromosomal abnormalities play a central role in the pathogenesis, diagnosis, and treatment monitoring of many hematologic disorders. Cytogenetic studies on bone marrow may be helpful in many malignant hematologic disorders as the observation of a chromosomally abnormal clone may be consistent with a neoplastic process. Certain chromosome abnormalities may help classify a malignancy. As examples, the Philadelphia (Ph) chromosome, also referred to as der(22)(t;9;22)(q34;q11.2), is usually indicative of chronic myeloid leukemia (CML) or acute leukemia; t(8;21)(q22;q22) defines a specific subset of patients with acute myeloid leukemia; and t(8;14)(q24.1;q32) is associated with Burkitt lymphoma. Cytogenetic studies are also used to monitor patients with hematologic neoplasia and may identify disease progression, such as the onset of blast crisis in CML, which is often characterized by trisomy 8, isochromosome 17q, and multiple Ph chromosomes. Conventional chromosome studies of B-cell disorders are not always successful because B lymphocytes do not proliferate well in cell culture. The agent CpG 7909 (CpG) is a synthetic oligodeoxynucleotide that binds to the Toll-like receptor 9 (TLR9) present on B cells, causing B-cell activation. In the laboratory setting, CpG may be used as a mitogen to stimulate B cells in patient specimens, thus allowing identification of chromosome abnormalities. CpG stimulation reveals an abnormal karyotype in approximately 80% of patients with chronic lymphocytic leukemia, and the karyotype is complex in 20% to 25% of cases. Several studies have reported that increased genetic complexity revealed by CpG-stimulated chromosome studies confers a less favorable time to first treatment, treatment response, and overall survival. See Diagnosis and Monitoring of Multiple Myeloma in Publications.

Useful For: Assisting in the diagnosis and classification of certain malignant hematological disorders Evaluating the prognosis in patients with certain malignant hematologic disorders Monitoring effects of treatment Monitoring patients in remission

Interpretation: To ensure the best interpretation, it is important to provide some clinical information to verify the appropriate type of cytogenetic study is performed. The following factors are important when interpreting the results: -Although the presence of an abnormal clone usually indicates a malignant neoplastic process, in rare situations, the clone may reflect a benign condition. -The absence of an abnormal clone may be the result of specimen collection from a site that is not involved in the neoplasm or may indicate that the disorder is caused by submicroscopic abnormalities that cannot be identified by chromosome analysis. -On rare occasions, the presence of an abnormality may be associated with a congenital abnormality that is not related to a malignant neoplastic process. Follow-up with a medical genetics consultation is recommended. -On occasion, bone marrow chromosome studies are unsuccessful. If clinical information has been provided, we may have a FISH study option that could be performed.

Reference Values: An interpretative report will be provided.


Chromosome Analysis, Hematologic Disorders, Fixed Cells

Clinical Information: Chromosomal abnormalities play a central role in the pathogenesis, diagnosis, and treatment monitoring of many hematologic disorders. Cytogenetic studies on bone marrow may be helpful in many malignant hematologic disorders as the observation of a
A chromosomally abnormal clone may be consistent with a neoplastic process. Certain chromosome abnormalities may help classify a malignancy. As examples, the Philadelphia (Ph) chromosome, also referred to as der(22)t(9;22)(q34;q11.2), is usually indicative of chronic myeloid leukemia (CML) or acute leukemia, t(8;21)(q22;q22) defines a specific subset of patients with acute myeloid leukemia, and t(8;14)(q24.1;q32) is associated with Burkitt lymphoma. Cytogenetic studies are also used to monitor patients with hematologic neoplasia and may identify disease progression, such as the onset of blast crisis in CML, which is often characterized by trisomy 8, isochromosome 17q, and multiple Ph chromosomes.

**Useful For:** Assisting in the diagnosis and classification of certain malignant hematological disorders Evaluating the prognosis of patients with certain malignant hematologic disorders Monitoring effects of treatment Monitoring patients in remission

**Interpretation:** To ensure the best interpretation, it is important to provide some clinical information to verify the appropriate type of cytogenetic study is performed. The following factors are important when interpreting the results: - Although the presence of an abnormal clone usually indicates a malignant neoplastic process, in rare situations, the clone may reflect a benign condition. - The absence of an abnormal clone may be the result of specimen collection from a site that is not involved in the neoplasm or may indicate that the disorder is caused by submicroscopic abnormalities that cannot be identified by chromosome analysis. - On rare occasions, the presence of an abnormality may be associated with a congenital abnormality that is not related to a malignant neoplastic process. Follow-up with a medical genetics consultation is recommended. - On occasion, bone marrow chromosome studies are unsuccessful. If clinical information has been provided, we may have a FISH study option that could be performed.

**Reference Values:**
An interpretative report will be provided.


**CHRLN 35309**

**Chromosome Analysis, Lymphoid Tissue**

**Clinical Information:** Chromosomal abnormalities play a central role in the pathogenesis, diagnosis, and monitoring of treatment of many hematologic disorders. The observation of a chromosomally abnormal clone is consistent with a clonal neoplastic process. Certain chromosome abnormalities can help classify the type of lymphoma. For example, t(14;18)(q32;q21.3) involving the IGH and BCL2 genes is usually indicative of a follicular lymphoma. A translocation between MYC and IGH genes or a t(8;14)(q24.1;q32) are both associated with Burkitt lymphoma. Cytogenetic studies often can help distinguish between B-cell and T-cell disorders. Structural abnormalities involving breakpoints at any immunoglobulin locus is consistent with a B-cell disorder; structural abnormalities involving breakpoints at a T-cell receptor site are usually associated with a T-cell disorder.

**Useful For:** Assisting in the classification of certain cases of lymphoma

**Interpretation:** The observation of a chromosomally abnormal clone is evidence of a clonal neoplastic process. Certain chromosome abnormalities also may be associated with certain morphologic classifications. However, a normal karyotype does not eliminate the possibility of a neoplastic process. On rare occasions, the presence of an abnormality may be associated with a congenital abnormality that is not related to a malignant neoplastic process. Follow-up with a medical genetics consultation is recommended.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:** 1. Pierre RV, Dewald GW, Banks PM: Cytogenetic studies in malignant...
**CRAT 35316**

**Chromosome Analysis, Rearrangement in Ataxia Telangiectasia, Blood**

**Clinical Information:** Chromosomal instability syndromes are autosomal recessive disorders characterized by defects in DNA repair mechanisms or genetic instability. Patients with these disorders have an increased risk of developing malignant disorders. When blood from affected individuals is cultured and chromosome analysis is performed, elevated rates of chromosomal rearrangements are observed. These disorders include ataxia telangiectasia (AT) and Nijmegen breakage syndrome (NBS). An increased frequency of chromosome rearrangements, including involvement at 7p13, 7q34, 14q11.2, or 14q32, signals a positive result. NBS usually has a higher frequency of cells with chromosome rearrangements than AT and generally does not include the clinical features of ataxia or increased serum alpha-fetoprotein. A normal result does not rule out a diagnosis of AT, NBS, or other chromosome instability syndromes.

**Useful For:** Evaluating patients for chromosome instability syndromes, including ataxia telangiectasia and Nijmegen breakage syndrome

**Interpretation:** The pattern of chromosome breakage and the number of breaks are compared to a normal control and an interpretive report is provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**BLOOM 35317**

**Chromosome Analysis, Sister Chromatid Exchange (SCE) for Bloom Syndrome, Blood**

**Clinical Information:** Sister chromatid exchange analysis is appropriate in individuals with clinical features suggestive of Bloom syndrome. Bloom syndrome is a genetic disorder associated with various congenital defects and predisposition to acute leukemia, pulmonary fibrosis, and Hodgkin lymphomas. Carcinoma also is commonly seen in these patients. Approximately one-fourth to one-half of patients develop some type of cancer with a mean age of 25 years at onset. The severity and age of onset of cancer varies among patients. These patients often have prenatal or postnatal growth retardation, short stature, malar hypoplasia, telangiectatic erythema of the face and other regions, hypopigmentation, immune deficiencies, occasional mild mental retardation, infertility, and high-pitched voices. Bloom syndrome is an autosomal recessive disorder caused by mutations in the BLM gene located at 15q26.1. While multiple mutations have been detected, the use of molecular testing to diagnose Bloom syndrome is limited in many ethnic groups. Patients with Bloom syndrome demonstrate a high frequency of chromosome abnormalities when their cells are cultured. Thus, cytogenetic studies can be helpful to establish a diagnosis. Bloom syndrome results in 2 characteristic cytogenetic abnormalities. First, the cells are at increased risk for random breaks leading to fragments or exchanges between nonhomologous chromosomes. Second, cells in these patients have an increased
frequency of sister chromatid exchanges (SCE: exchange of material between homologous chromosomes) of approximately 10-fold to 20-fold higher than average. This test is diagnostic for Bloom syndrome. This test cannot be used to identify heterozygote carriers for Bloom syndrome and is not appropriate as part of a prenatal screening panel. A normal result does not rule out the possibility of birth defects, such as those caused by chromosomal abnormalities, molecular mutations, and environmental factors (ie, teratogen exposure). The test does not rule out other numeric or structural abnormalities. If a constitutional chromosome abnormality is suspected, a separate conventional cytogenetic study, CHRCB / Chromosome Analysis, for Congenital Disorders, Blood should be requested.

**Useful For:** Establishing a diagnosis of Bloom syndrome

**Interpretation:** A frequency of sister chromatid exchange comparable to a control specimen and historical reference values will be reported as normal. A 10-fold or more increase in sister chromatid exchange relative to a control specimen and historical reference values will be reported as abnormal. This is consistent with a diagnosis of Bloom syndrome.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**CHRTI 35250**

**Chromosome Analysis, Skin Biopsy**

**Clinical Information:** Chromosomal abnormalities cause a wide range of disorders associated with birth defects and congenital diseases. Usually, the abnormalities can be demonstrated in peripheral blood, which is readily available. Chromosome analysis on skin fibroblasts may be indicated when the results from peripheral blood are inconclusive or in clinical circumstances such as suspected cases of chromosome mosaicism, confirmation of new chromosome disorders, or some dermatological disorders. Subtle structural chromosomal anomalies can occasionally be missed. Chromosomal mosaicism may be missed due to statistical sampling error (rare).

**Useful For:** Diagnosis of mosaic congenital chromosome abnormalities, including mosaic aneuploidy and mosaic structural abnormalities Subsequent chromosome analysis when results from peripheral blood are inconclusive

**Interpretation:** When interpreting results, the following factors need to be considered: -Some chromosome abnormalities are balanced (no apparent gain or loss of genetic material) and may not be associated with birth defects. However, balanced abnormalities often cause infertility and, when inherited in an unbalanced fashion, may result in birth defects in the offspring. -A normal karyotype (46,XX or 46,XY with no apparent chromosome abnormality) does not eliminate the possibility of birth defects such as those caused by submicroscopic cytogenetic abnormalities, molecular mutations, and environmental factors (ie, teratogen exposure). It is recommended that a qualified professional in Medical Genetics communicate all results to the patient.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
**Chromosome Analysis, Solid Tumors**

**Clinical Information:** Most malignant neoplasms are associated with clonal genetic abnormalities and the observation of an abnormal cytogenetic clone is consistent with a neoplasm. In many instances, these abnormalities can be demonstrated by cytogenetic analysis. Some physicians now consider cytogenetic analysis a useful laboratory test to determine the neoplastic potential of solid tumors. For some tumors, cytogenetic analysis can help classify solid tumors. For example, an X;18 translocation has been specifically associated with synovial sarcoma, many alveolar rhabdomyosarcomas have an associated 2;13 translocation, and nearly every myxoid liposarcoma has a 12;16 translocation. A complete summary of the correlation between tumor histology and specific chromosome anomalies is too extensive to summarize here. The reader is referred to the Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer. 2014 Available at URL: http://cgap.nci.nih.gov/Chromosomes/Mitelman

**Useful For:** Assisting in the classification of malignant tumors associated with chromosomal abnormalities

**Interpretation:** The observation of a chromosomally abnormal clone is evidence of a clonal neoplastic process. Certain chromosome abnormalities may also be specifically associated with certain morphologic classifications. In many tumors, the cytogenetic interpretation may be complicated by the observation of numerous complex chromosome anomalies. Nevertheless, the presence of certain chromosome abnormalities within a complex karyotype may still aid in classifying the tumor. However, a normal karyotype does not eliminate the possibility of a neoplastic process. Additionally, FISH testing or other strategies may be more appropriate for certain tumor types. On rare occasions, the presence of an abnormality may be associated with a congenital abnormality that is not related to a malignant neoplastic process. Follow-up with a medical genetics consultation is recommended.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Chronic Hepatitis (Unknown Type)**

**Clinical Information:** Hepatitis B: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (eg, blood transfusion, sharing of needles by drug addicts). The virus is also found in virtually every type of human body fluid and is known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions; it is not commonly transmitted transplacentally. After a course of acute illness, HBV persists in approximately 10% of patients. Some of these carriers are asymptomatic, others develop chronic liver disease including cirrhosis and hepatocellular carcinoma. Hepatitis C: Hepatitis C virus (HCV) is an RNA virus that is a significant cause of morbidity and mortality worldwide. HCV is transmitted through contaminated blood or blood products or through other close, personal contacts. It is recognized as the cause of most cases of posttransfusion hepatitis. HCV shows a high rate of progression (>50%) to chronic disease. In the United States, HCV infection is quite common, with an estimated 3.5 to 4 million chronic HCV carriers. Cirrhosis and hepatocellular carcinoma are sequelae of chronic HCV.

The following algorithms are available in Special Instructions: -Hepatitis C: Testing Algorithm for Screening and Diagnosis -Chronic Hepatitis C Treatment and Monitoring Algorithm: Direct Antiviral Antigen (DAA) Combination (Interferon-Free) -Viral Hepatitis Serologic Profiles -HBV Infection-Diagnostic Approach and Management Algorithm

**Useful For:** Diagnosis and evaluation of patients with symptoms of hepatitis with a duration more
than 6 months Distinguishing between chronic hepatitis B and chronic hepatitis C

**Interpretation:** Interpretation depends on clinical setting. See Viral Hepatitis Serologic Profile in Special Instructions. Chronic Hepatitis B: Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum 6 to 16 weeks following hepatitis B viral infection. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6 months indicates development of either a chronic carrier state or chronic liver disease. Anti-hepatitis B core (anti-HBc) appears shortly after the onset of symptoms. The IgM subclass usually falls to undetectable levels within 6 months, and the IgG subclass may remain for many years. Hepatitis B surface antibody (anti-HBs) usually appears with the resolution of hepatitis B virus infection after the disappearance of HBsAg. If HBsAg and anti-HBc (total antibody) are positive and patient's condition warrants, consider testing for hepatitis Be antigen (HBeAg), anti-HBe, hepatitis B virus DNA (HBV-DNA) or anti-hepatitis D virus (anti-HDV). Chronic Hepatitis C Virus (HCV): Anti-HCV is almost always detectable by the late convalescent and chronic stage of infection. The serologic tests currently available do not differentiate between acute and chronic hepatitis C infections.

**Reference Values:**

**HEPATITIS B SURFACE ANTIGEN**
Negative

**HEPATITIS B SURFACE ANTIBODY, QUALITATIVE/QUANTITATIVE**

- Hepatitis B Surface Antibody
  - Unvaccinated: negative
  - Vaccinated: positive

- Hepatitis B Surface Antibody, Quantitative
  - Unvaccinated: <5.0 mIU/mL
  - Vaccinated: > or =12.0 mIU/mL

**HEPATITIS B CORE TOTAL ANTIBODIES**
Negative

**HEPATITIS C ANTIBODY**
Negative

Interpretation depends on clinical setting.

**Clinical References:**

**CHSBP 9023**

**Chronic Hepatitis Profile (Type B)**

**Clinical Information:** Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (eg, blood transfusion and sharing of needles by drug addicts). The virus is also found in virtually every type of human body fluid and is known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions; it is not commonly transmitted transplacentally. After a course of acute illness, HBV persists in approximately 10% of patients. Some of these carriers are asymptomatic; others develop chronic liver disease including cirrhosis and hepatocellular carcinoma. See HBV Infection-Diagnostic Approach and Management Algorithm and Viral Hepatitis Serologic Profile in Special Instructions.

**Useful For:** Evaluating patients with suspected or confirmed chronic hepatitis B Monitoring hepatitis B viral infectivity
**Interpretation:** Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum 6 to 16 weeks following hepatitis B viral (HBV) infection. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6 months indicates development of either chronic carrier state or chronic liver disease. Hepatitis B surface antibody (anti-HBs) appears with the resolution of HBV infection after the disappearance of HBsAg. Anti-HBs also appears as the immune response following a course of inoculation with the hepatitis B vaccine. Hepatitis B core antibody (anti-HBc) appears shortly after the onset of symptoms of HBV infection and may be the only serologic marker remaining years after exposure to hepatitis B. The presence of hepatitis Be antigen (HBeAg) correlates with infectivity, the number of viral Dane particles, the presence of core antigen in the nucleus of the hepatocyte, and the presence of viral DNA polymerase in serum. Hepatitis Be antibody (anti-HBe) positivity in a carrier is often associated with chronic asymptomatic infection. If the patient has a sudden exacerbation of disease, consider ordering hepatitis C virus antibody (anti-HCV) and hepatitis delta virus antibody (anti-HDV). If HBsAg converts to negative and patient’s condition warrants, consider testing for anti-HBs. If HBsAg is positive, consider testing for anti-HDV.

**Reference Values:**

**HEPATITIS B SURFACE ANTIGEN**

Negative

**HEPATITIS Be ANTIGEN**

Negative

**HEPATITIS Be ANTIBODY** Negative

Interpretation depends on clinical setting. See Viral Hepatitis Serologic Profiles in Special Instructions.

**Clinical References:**


**CLLMV**

65175

**Chronic Lymphocytic Leukemia (CLL) Monitoring Minimal Residual Disease (MRD) Detection, Varies**

**Clinical Information:** Chronic lymphocytic leukemia (CLL) is a low-grade, B-cell neoplasm that is the most common leukemia detected in the western world. It is a disease primarily of adults and may present as a lymphocytosis, be detected as part of a lymphadenopathy evaluation, or be found incidentally in an otherwise asymptomatic patient. The diagnosis of CLL is based on a combination of morphologic features showing primarily small lymphoid cells with coarse chromatin and scant cytoplasm and an immunophenotype of clonal B-cells with dim immunoglobulin, dim CD20, and coexpression of CD5 and CD23. New therapeutic approaches in CLL have been increasingly successful with some patients showing no or only very minimal residual disease (MRD) in their peripheral blood or bone marrow specimens following a therapeutic course. Immunophenotyping studies are necessary as morphologic features are not sufficient to detect MRD. The absence of MRD is an important prognostic indicator in these patients.

**Useful For:** Confirming the presence or absence of minimal residual disease in patients with known chronic lymphocytic leukemia who are either postchemotherapy or post-bone marrow transplantation

**Interpretation:** An interpretive report for presence or absence of minimal residual disease (MRD) for chronic lymphocytic leukemia (CLL) is provided. Individuals without CLL should not have detectable clonal B cells in the peripheral blood or bone marrow. Patients who have detectable MRD by this assay are considered to have residual CLL disease.
Reference Values:
An interpretive report will be provided.

This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and correlation with the morphologic features will be provided by a hematopathologist for every case.


CLL  
Chronic Lymphocytic Leukemia (CLL), FISH

Clinical Information: Chronic lymphocytic leukemia (CLL) is the most common leukemia in North America. The most common cytogenetic abnormalities in CLL involve chromosomes 6, 11, 12, 13, and 17. These are detected and quantified using the CLL FISH panel. Use of CpG-oligonucleotide mitogen will identify an abnormal CLL karyotype in at least 80% of cases. This mitogen is added to cultures when chromosome analysis is ordered and the reason for referral is a B-cell disorder (CHRBM / Chromosome Analysis, Hematologic Disorders, Bone Marrow and CHRHB / Chromosome Analysis, Hematologic Disorders, Blood). This FISH test detects an abnormal clone in approximately 70% of patients with indolent disease and >80% of patients who require treatment. At least 5% of patients referred for CLL FISH testing have translocations involving the IGH locus; approximately 66% of these patients have translocations that result in fusion of IGH/CCND1, IGH/BCL2, or IGH/BCL3. Fusion of IGH and CCND1 is associated with t(11;14)(q13;q32), IGH and BCL2 with t(14;18)(q32;q21), and IGH and BCL3 with t(14;19)(q32;q13.3). Patients with t(11;14)(q13;q32) usually have the leukemic phase of mantle cell lymphoma. Patients with t(14;18) or t(14;19) may have an atypical form of B-CLL or the leukemic phase of a lymphoma. The prognostic associations for chromosome abnormalities detected by this FISH assay are, from best to worst: 13q-, normal, +12, 6q-, 11q-, and 17p-.

Useful For: Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with chronic lymphocytic leukemia (CLL) Identifying and tracking known chromosome abnormalities in patients with CLL and tracking response to therapy Distinguishing patients with 11;14 translocations who have leukemic phase of mantle cell lymphoma from patients who have CLL Detecting patients with atypical CLL or other forms of lymphoma associated with translocations between IGH and BCL2, BCL3, MYC, or other partner genes

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe set. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.


Chub Mackerel, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>&gt; or =100</td>
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Chyluria Screen

Clinical Information: Chyle is lymphatic fluid that contains emulsified fats (chylomicrons). Chyle in the urine (chyluria) is the result of obstruction of lymph flow and rupture of lymphatic vessels into the renal tubules. Chyluria, also called galacturia, imparts a milky appearance to urine.
Useful For: Diagnosis of chyluria (galacturia)

Interpretation: This assay provides information regarding the fat content in urine fluid. Urinary cholesterol and triglyceride values are normally <10 mg/dL. High triglycerides in urine may indicate chyluria.

Reference Values:
No lipoproteins present


Chymopapain, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Chymotrypsin, Stool

Reference Values:
2.3 – 51.4 U/g

Cinnamon IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Cinnamon, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
**Circulating Immune Complexes (CIC)**

**Interpretation:** Circulating immune complexes (CICs) are detectable in a variety of systemic disorders such as rheumatological, autoimmune, allergic diseases; viral, bacterial infections and malignancies. Although detection of CICs is neither essential nor specific for any disease, anti-C1q assay is likely to provide information regarding disease activity in lupus nephritis.

**Reference Values:**
- Negative: <20 EU/mL
- Borderline/Equivocal: 20 – 25 EU/mL
- Positive: >25 EU/mL

**Circulating Tumor Cells (CTC) for Breast Cancer by CellSearch, Blood**

**Clinical Information:** In patients with metastatic cancer, tumor cells may be present in the bloodstream (circulating tumor cells: CTCs). Studies suggest that the number of CTCs is associated with progression-free and overall survival in patients with metastatic breast cancer. Serial testing for CTCs, in conjunction with other clinical methods for monitoring breast cancer, can assist physicians in the management of these patients.

**Useful For:** Aids in monitoring patients with metastatic breast cancer

**Interpretation:** Results are reported as favorable or unfavorable. In patients with metastatic breast cancer, unfavorable results (> or =5 circulating tumor cells/7.5 mL of blood) are predictive of shorter progression-free survival and shorter overall survival.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
**CTCPC**

**Circulating Tumor Cells (CTC) for Prostate Cancer by CellSearch, Blood**

**Clinical Information:** According to the American Cancer Society, prostate cancer claims approximately 28,000 lives each year, the vast majority of which are a result of metastatic disease. Although there are many options for the treatment of metastatic prostate cancer, oncologists often have to wait several months after initiation of treatment before they can determine if the treatment is beneficial to the patient. The CellSearch System identifies and enumerates the number of circulating tumor cells (CTCs) in a blood specimen. (1) Studies suggest that the number of CTCs is associated with progression-free and overall survival in patients with metastatic prostate cancer. (2,3)

**Useful For:** Aids in monitoring patients with metastatic prostate cancer

**Interpretation:** Results are reported as favorable or unfavorable. In patients with metastatic prostate cancer, the finding of > or =5 circulating tumor cells/7.5 mL of blood is predictive of shorter progression-free survival and overall survival. (2)

**Reference Values:** An interpretive report will be provided.


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**CITAL**

**Citalopram, Serum**

**Clinical Information:** Citalopram (Celexa) and S-citalopram (escitalopram, Lexapro) are approved for treatment of depression. Celexa is a racemic mixture containing equal amounts of R- and S-enantiomer. Metabolites of citalopram (N-desmethylcitalopram) are less active than citalopram and do not accumulate in serum to clinically significant concentration. Citalopram metabolism is carried out by cytochrome P450 (CYP) 2C19 and 3A4-5. CYP 2D6 may play a minor role in citalopram metabolism. Citalopram is known to reduce CYP 2D6 activity. Citalopram clearance is significantly affected by reduced hepatic function, but only slightly by reduced renal function. A typical Celexa dose administered to an adult is 40-mg per day. A typical Lexapro dose is 20-mg per day. Citalopram is 80% protein bound, and the apparent volume of distribution is 12 L/Kg. Bioavailability is 80% and protein binding is 56% for either form of the drug. Time to peak serum concentration is 4 hours, and the...
elimination half-life is 35 hours. Half-life is increased in the elderly. Dosage reductions may be necessary for patients who are elderly or have reduced hepatic function.

**Useful For:** Monitoring citalopram therapy Identifying noncompliance, although regular blood level monitoring is not indicated in most patients Identifying states of altered drug metabolism when used in conjunction with CYP2C19 and CYP3A4-5 genotyping

**Interpretation:** Steady-state serum concentrations associated with optimal response to citalopram are in the range of 50 to 100 ng/mL when the patient is administered the R,S-enantiomeric mixture (Celexa). The most common toxicities associated with excessive serum concentration are fatigue, impotence, insomnia, and anticholinergic effects. The toxic range for citalopram is >220 ng/mL.

**Reference Values:**
50-110 ng/mL

**Clinical References:**

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**Citrate Excretion, 24 Hour, Urine**

**Clinical Information:** Urinary citrate is a major inhibitor of kidney stone formation due in part to binding of calcium in urine. Low urine citrate levels are considered a risk for kidney stone formation. Several metabolic disorders are associated with low urine citrate. Any condition that lowers renal tubular pH or intracellular pH may decrease citrate (eg, metabolic acidosis, increased acid ingestion, hypokalemia, or hypomagnesemia). Low urinary citrate promotes kidney stone formation and growth, and is subject to therapy by correcting acidosis, hypokalemia, or hypomagnesemia by altering diet or using drugs such as citrate and potassium.

**Useful For:** Diagnosing risk factors for patients with calcium kidney stones Monitoring results of therapy in patients with calcium stones or renal tubular acidosis

**Interpretation:** Any value less than the mean for 24 hours represents a potential risk for kidney stone formation and growth. Patients with low urinary citrate, and new or growing stone formation, may benefit from adjustments in therapy known to increase urinary citrate excretion. (See Clinical Information) Very low levels (<150 mg/24 hours) suggest investigation for the possible diagnosis of metabolic acidosis (eg, renal tubular acidosis).

**Reference Values:**
0-19 years: not established
20 years: 150-1,191 mg/24 hours
21 years: 157-1,191 mg/24 hours
22 years: 164-1,191 mg/24 hours
23 years: 171-1,191 mg/24 hours
24 years: 178-1,191 mg/24 hours
25 years: 186-1,191 mg/24 hours
26 years: 193-1,191 mg/24 hours
27 years: 200-1,191 mg/24 hours
28 years: 207-1,191 mg/24 hours
29 years: 214-1,191 mg/24 hours
30 years: 221-1,191 mg/24 hours
31 years: 228-1,191 mg/24 hours
32 years: 235-1,191 mg/24 hours
33 years: 242-1,191 mg/24 hours
34 years: 250-1,191 mg/24 hours
35 years: 257-1,191 mg/24 hours
36 years: 264-1,191 mg/24 hours
37 years: 271-1,191 mg/24 hours

**Citrate Excretion, Pediatric, Random, Urine**

**Clinical Information:** Urinary citrate is a major inhibitor of kidney stone formation due in part to binding of calcium in urine. Low urine citrate levels are considered a risk for kidney stone formation. Several metabolic disorders are associated with low urine citrate. Any condition which lowers renal tubular pH or intracellular pH may decrease citrate (eg, metabolic acidosis, increased acid ingestion, hypokalemia, or hypomagnesemia). Low urinary citrate is subject to therapy by correcting acidosis, hypokalemia, or hypomagnesemia by altering diet or using drugs such as citrate and potassium.

**Useful For:** Diagnosing risk factors for patients with calcium kidney stones. Monitoring results of therapy in patients with calcium stones or renal tubular acidosis. A timed 24-hour urine collection is the preferred specimen for measuring and interpreting this urinary analyte. Random collections normalized to urinary creatinine may be of some clinical use in patients who cannot collect a 24-hour specimen, typically small children. Therefore, this random test is offered for children <16 years old.

**Interpretation:** A low value represents a potential risk for kidney stone formation/growth. Patients with low urinary citrate, and new or growing stone formation may benefit from adjustments in therapy known to increase urinary citrate excretion. Very low levels suggest investigation for the possible diagnosis of metabolic acidosis (eg, renal tubular acidosis). For children ages 5 to 18, a ratio of <0.176 mg citrate/ mg creatinine is below the 5% reference range and considered low.(1)

**Reference Values:**
No established reference values

**Cladosporium, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Clam, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**Reference values apply to all ages.**


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**Claudin-1 Immunostain, Technical Component Only**

**Clinical Information:** Claudins are a family of tight junction-associated proteins that prevent leakage of ions, water, etc, between cells. Differential expression of claudin proteins is seen in various epithelial cell types. Strong expression of claudin-1 is seen on squamous epithelial cells of the skin. Claudin-1 may have reduced expression in invasive versus benign breast lesions. In the diagnostic setting, 30% to 50% of soft tissue and intramuscular intestinal perineuriomas are positive for claudin-1. Gastric intestinal-type adenocarcinoma shows more frequent claudin-1 expression than diffuse gastric carcinomas.

**Useful For:** Aids in the identification of a number of different soft tissue and epithelial neoplasms

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the
context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**FCLCN**

**CLCN1 DNA Sequencing Test**

**Reference Values:**
A final report will be attached in MayoAccess.

**FCLBZ**

**Clobazam, Serum/Plasma**

**Reference Values:**
Clobazam: 30 - 300 ng/mL
Desmethylclobazam: 300 - 3000 ng/mL

**CLOM**

**Clomipramine, Serum**

**Clinical Information:** Clomipramine (chlorimipramine, Anafranil) is a tricyclic antidepressant drug used primarily to treat obsessive-compulsive disorder (OCD). Clomipramine is also used to treat panic disorder and treatment-resistant depression. Clomipramine preferentially blocks synaptic reuptake of serotonin; its pharmacologically active metabolite, norclomipramine (desmethylchlorimipramine) preferentially blocks synaptic reuptake of norepinephrine. Clomipramine undergoes significant first-pass hepatic metabolism (up to 50%) which probably explains the high degree of interindividual variability observed between administered dose and steady-state serum concentrations of the drug and its metabolite. The serum ratio of clomipramine to norclomipramine is typically 1:2-2.5. The elimination half-lives of clomipramine and norclomipramine are 19-37 hours and 54-77 hours, respectively. One to two weeks are required to achieve steady-state when a patient is started on clomipramine or following an alteration in the dose. Anticholinergic side effects (ie, dry mouth, excessive sweating, blurred vision, urinary retention, constipation) frequently accompany treatment. Other side effects may include tremor, nausea, orthostatic hypotension, dizziness, sexual dysfunction, and sleep disturbances. Signs and symptoms following overdose are similar to other tricyclic antidepressant drugs: cardiac toxicity (eg, tachycardia, arrhythmia, impaired conduction, congestive heart failure) is the major concern.

**Useful For:** Determining whether a poor therapeutic response is attributable to noncompliance
Monitoring serum concentration of clomipramine and norclomipramine to assist in optimizing the administered dose

**Interpretation:** Studies investigating the relationship between serum concentrations of clomipramine and norclomipramine and therapeutic response have yielded conflicting results. However, the probability of therapeutic failure seems to increase if the sum of the clomipramine and norclomipramine serum concentrations is <230 ng/mL. Summed serum concentrations of clomipramine and norclomipramine...
which exceed 450 ng/mL seem to result in no additional enhancement in therapeutic response and may predispose the patient to greater risk of adverse side affects. A toxic range has not been well established at this time.

**Reference Values:**
CLOMIPRAMINE AND NORCLOMIPRAMINE
Therapeutic concentration: 230-450 ng/mL

Note: Therapeutic ranges are for specimens drawn at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.

**Clinical References:**

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**Clonazepam and 7-Aminoclonazepam, Serum**

**Clinical Information:** Clonazepam [5 (2-chlorophenyl)-2, 3-dihydro-7-nitro-1, 4-benzodiazepin-2-one,] a benzodiazepine is useful alone or as an adjunct in the treatment of certain seizures. In addition, it may be useful in patients with panic disorder, and restless legs syndrome. Clonazepam has no definite antiseizure and antipanic mechanism of action, although it is believed to be related to its capacity to enhance gamma-aminobutyric acid (GABA) activity, which is the major inhibitory neurotransmitter in the central nervous system. It is able to suppress the spike and wave discharges in absence seizures and decrease the frequency, duration, amplitude and spread of discharge in minor motor seizures. Clonazepam is highly protein bound (approximately 85%). It is extensively metabolized by hepatic: P450 CYP3A, to inactive metabolites, and has a half-life of 30 to 40 hours.

**Useful For:** Assessing compliance Monitoring for appropriate therapeutic level Assessing toxicity

**Interpretation:** The therapeutic range varies depending on the indication. Some individuals may respond well outside of these ranges, or may display toxicity within the therapeutic range, thus interpretation should include clinical evaluation. The possibility of toxicity is increased when levels exceed 100 ng/mL. Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next dose).

**Reference Values:**
Clonazepam
- Anticonvulsant: 20-70 ng/mL
- Anxiolytic: 4-80 ng/mL

Some individuals may show therapeutic response outside of these ranges, or may display toxicity within the therapeutic range, thus interpretation should include clinical evaluation.

Note: Therapeutic ranges are for specimens drawn at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.

**Clinical References:**

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**Clonidine (Catapres)**

**Reference Values:**
Reference Range: 1.00 - 2.00 ng/mL

Sedation has been associated with serum clonidine concentrations greater than 1.5 ng/mL

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Current as of October 11, 2018 2:20 pm CDT   800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  Page 571
Toxic concentration has not been established.

**Clostridioides (Clostridium) difficile Toxin, Molecular Detection, PCR, Feces**

**Clinical Information:** Clostridioides (Clostridium) difficile is the cause of C difficile-associated diarrhea (CDAD), an antibiotic-associated diarrhea, and pseudomembranous colitis (PMC). In these disorders bacterial overgrowth of C difficile develops in the colon, typically as a consequence of antibiotic usage. Clindamycin and broad-spectrum cephalosporins have been most frequently associated with CDAD and PMC, but almost all antimicrobials may be responsible. Disease is related to production of toxin A and B. Treatment typically involves withdrawal of the associated antimicrobials and, if symptoms persist, orally administered and intraluminally active metronidazole, vancomycin, or fidaxomicin. Intravenous metronidazole may be used if an oral agent cannot be administered. In recent years, a more severe form of CDAD with increased morbidity and mortality has been recognized as being caused by an epidemic toxin-hyperproducing strain of C difficile (NAP1 strain). Many toxin-hyperproducing isolates also contain the binary toxin gene and are resistant quinolones. This test does not differentiate between toxin-hyperproducing and nontoxin-hyperproducing strains. Traditionally, diagnosis relied upon 1) clinical and epidemiologic features, 2) culture (which is labor intensive and time consuming), 3) cytotoxicity assays, which are labor intensive and time consuming, and 4) toxin detection immunoassays (which are insensitive). The described PCR assay detects the regulatory gene (tcdC) responsible for production of toxins A and B. This test is used for rapid diagnosis of CDAD and PMC enabling prompt treatment that may reduce hospital stays for inpatients with CDAD.

**Interpretation:** A positive PCR result for the presence of the gene regulating toxin production (tcdC) indicates the presence of Clostridioides (Clostridium) difficile and toxin A and/or B. A negative result indicates the absence of detectable C difficile tcdC DNA in the specimen, but does not rule-out C difficile infection. False-negative results may occur due to inhibition of PCR, sequence variability underlying the primers or probes, or the presence of C difficile in quantities less than the limit of detection of the assay.

**Reference Values:**
Not applicable

**Clinical References:**

**Clostridium difficile Culture**

**Clinical Information:** Clostridium difficile can cause diarrhea, and may cause pseudomembranous colitis. Overgrowth of toxin-producing C difficile in the colon leads to the production of toxins A and/or B by the organism, and consequent diarrhea. C difficile infection should be suspected in patients with symptoms of diarrhea with risk factors such as current or recent use of antibiotics, a history of C difficile infection, current or recent hospitalization or placement in a nursing home or long-term care facility, age older than 65 years, gastric acid suppression, etc. C difficile infection is the most common cause of diarrhea in hospitalized patients and may lead to serious complications, including sepsis, bowel perforation, and increased overall mortality (especially in elderly patients). The incidence of C difficile infection has not been established.
infection has risen in the community and in healthcare settings. While culture is not the preferred means to diagnose C difficile-associated diarrhea, culture for C difficile provides an isolate suitable for antimicrobial susceptibility testing. Note that this test does not differentiate between toxin-producing and nontoxicogenic strains of C difficile.

**Useful For:** Clostridium difficile culture provides an isolate suitable for antimicrobial susceptibility testing.

**Interpretation:** A positive result indicates the presence of viable Clostridium difficile in stool. A positive culture may be found with asymptomatic Clostridium difficile colonization with a toxin-producing or non-toxin-producing strain, or with Clostridium difficile-associated diarrhea. A negative result indicates the absence of Clostridium difficile growth in culture. Isolation of Clostridium difficile does not differentiate between toxin-producing and non-toxin-producing strains.

**Reference Values:**
No growth after 1 day of incubation.

**Clinical References:** Cohen SH, Gerding DN, Johnson S, et al: Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol 2010;31(5):431-455

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**CLOV 82490**

**Clove, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
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<td>Positive</td>
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<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

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### Clozapine, Serum

**Clinical Information**: Clozapine (Clozaril), a tricyclic dibenzodiazepine, is used for the symptomatic management of psychotic disorders and is considered an atypical antipsychotic drug. It is currently used primarily for the treatment of patients with schizophrenia or schizoaffective disorders who are at risk for recurrent suicidal behavior and who have encountered nonresponse or adverse, intolerable extrapyramidal side effects with more classical antipsychotics (chlorpromazine, haloperidol). Although clozapine was developed about 30 years ago and the initial results were promising, the development of several fatal cases of agranulocytosis resulted in the discontinued use of this agent. Seizures, an increased risk of fatal myocarditis, and orthostatic hypotension have also been associated with the use of clozapine. The use of clozapine has regained interest for several reasons. Patients who did not respond to treatment with other antipsychotics improved when clozapine was administered. Also, the agranulocytosis that occurs in approximately 1% to 2% of patients can be controlled with close hematologic monitoring. However, because of the significant risk of agranulocytosis and seizure associated with its use, clozapine should only be used in patients who have failed to respond adequately to treatment with appropriate courses of standard drug treatments, either because of insufficient effectiveness or the inability to achieve an effective dose because of intolerable adverse reactions from those drugs. Treatment is usually started with dosages of 25 to 75 mg/day with a gradual increase to reach a final dose of 300 to 450 mg/day within approximately 2 weeks of the initiation of treatment. Once the desired effect is achieved, the dose may be gradually decreased to keep the patient on the lowest possible effective dose. Patients being treated with clozapine should be closely monitored during treatment for adverse reactions. Treatment must include monitoring of white blood cell count and absolute neutrophil count. Clozapine treatment should be discontinued in patients failing to show an acceptable clinical response. In addition, in patients exhibiting beneficial clinical responses, the need for continuing treatment should be periodically reevaluated. Clozapine is metabolized to desmethylated and N-oxide derivatives. The desmethyl metabolite (norclozapine) has only limited activity, and N-oxide metabolite is inactive.

**Useful For**: Monitoring patient compliance An aid to achieving desired plasma levels

**Interpretation**: The effectiveness of clozapine treatment should be based on clinical response and treatment should be discontinued in patients failing to show an acceptable clinical response.

**Reference Values**:

<table>
<thead>
<tr>
<th>Component</th>
<th>Therapeutic range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLOZAPINE</td>
<td>&gt;350 ng/mL</td>
</tr>
<tr>
<td>CLOZAPINE + NORCLOZAPINE</td>
<td>&gt;450 ng/mL</td>
</tr>
</tbody>
</table>

Clusterin Immunostain, Technical Component Only

**Clinical Information:** In lymph nodes, tonsils, and spleen, clusterin stains the follicular dendritic cell meshworks. B cells, T cells, and histiocytes are negative. Clusterin is often positive in the tumor cells of systemic anaplastic large-cell lymphoma and is usually negative in Reed Sternberg cells in classical Hodgkin lymphoma. It is a sensitive marker for follicular dendritic cell sarcomas.

**Useful For:** A marker of follicular dendritic cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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cMET Immunostain, Technical Component Only

**Clinical Information:** c-Met, a cell surface receptor tyrosine kinase, regulates cellular proliferation, migration, and differentiation during development. Increased expression of c-Met has been shown to correlate with poor prognosis in nonsmall cell carcinomas of the lung.

**Useful For:** Aids in the identification of normal and neoplastic c-Met expressing cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
**CMV by PCR**

**Reference Values:**
- Not detected = Negative, no virus detected
- Detected = Positive, virus detected
- <1000 copies/mL = Positive. Virus detected below 1000 copies/mL
- 1000 copies/mL to 1,000,000 copies/mL = Positive
- >1,000,000 copies/mL = Positive. Virus detected above maximum quantitative range.

This test employs real-time PCR amplification of a Cytomegalovirus-specific conserved genetic target. A positive result should be coupled with clinical indicators for diagnosis. A “Not detected” result for this assay does not exclude Cytomegalovirus involvement in a disease process.

**CNBP DNA Test (DM2)**

**Clinical Information:** Detects CCTG repeat expansions in the Zinc Finger Protein 9 (ZNF9) gene.

**Typical Presentation:** Individuals with a range of symptoms from cataracts to significant muscle wasting, cardiac complications, ptosis and myotonia.

**Reference Values:**
A final report will be attached in MayoAccess.

**CNS Demyelinating Disease Evaluation, Serum**

**Clinical Information:** Neuromyelitis optica (NMO), sometimes called Devic disease or opticospinal multiple sclerosis (MS) is a severe, relapsing, autoimmune, inflammatory and demyelinating central nervous system disease (IDD) that predominantly affects optic nerves and spinal cord. The disorder is now recognized as a spectrum of autoimmunity (termed NMO spectrum disorders: NMOSD).(1-3) Brain lesions are observed in more than 60% of patients with NMOSD and approximately 10% will be MS-like.(4) Children tend to have greater brain involvement than adults, and brain lesions are more symptomatic than is typical for adult patients.(3) The clinical course is characterized by relapses of optic neuritis or transverse myelitis, or both. Some patients may present with acute disseminated encephalomyelitis (ADEM). Many patients with NMOSD are misdiagnosed as having MS. More effective treatments combined with earlier and more accurate diagnosis has led to improved outcomes. Approximately 80% of patients with NMO are seropositive for aquaporin-4 (AQP4)-IgG.(5-7) In the remaining 20% of patients, myelin oligodendrocyte glycoprotein (MOG)-IgG is detected in up to a third.(8) The pathogenic target for the remaining patients remains unknown. Detection of MOG-IgG is diagnostic of central nervous system (CNS) inflammatory demyelination, where the clinical phenotype (NMOSD, optic neuritis, transverse myelitis, ADEM) may be similar, but the immunopathology (astrocytopathy vs oligodendrogliopathy) and clinical outcome (worse vs better) is different.(9) Detection of MOG-IgG also predicts relapse.(10) More importantly, however, is that MOG-IgG seropositive IDDs are distinct from MS and treated differently. (8, 9) Treatments for IDDs seropositive for MOG-IgG include corticosteroids and plasmapheresis for acute attacks and mycophenolate mofetil, azathioprine, and rituximab for relapse prevention. Disease modifying agents, treatments promoted for MS, have been reported to exacerbate MOG-IgG1 seropositive IDDS. Therefore, early diagnosis and initiation of appropriate immunosuppressant treatment is important to optimize the clinical outcome by preventing further attacks. In 2015, Waters and colleagues (11) from Oxford University established a novel cell based assay for the measurement of IgG1 MOG antibodies based on previous findings that MOG antibodies are almost exclusively of the IgG1 subclass. They showed that their MOG-IgG1 flow cytometry assay eliminated false-positives without losing true-positives with low titers. The detection of MOG-IgG1 allowed non MS demyelinating diseases (ADEM, AQP4-IgG negative neuromyelitis optica spectrum disorder: including ON,TM) to be distinguished from MS.(12) Using a similar assay to our MOG-IgG1 flow cytometry assay, Wingerchuk et al demonstrated high specificity of their MOG-IgG1 assay in which 49 patients with MS, 13 healthy control sera, and 37 AQP4-seropositive serum samples were all negative at a dilution of 1:20. Of 58 patients fulfilling 2006 Wingerchuk criteria for NMO, 21 (36%) tested
negative for AQP4-IgG MOG-IgG1 was detected by cell based assay in 8 (38%) of these cases. (13) Testing of 1,109 consecutive sera sent for AQP4-IgG testing,(11) revealed 40 AQP4-IgG and 65 MOG-IgG1 positive cases. None were positive for both. The clinical diagnoses obtained in 33 MOG-IgG1 positive patients included 4 NMO, 1 ADEM and 11 optic neuritis (n = 11). All 7 patients with probable MS were MOG-IgG1 negative. This study provides Class II evidence that the presence of serum MOG-IgG1 distinguishes non-MS central nervous system (CNS) demyelinating disorders from MS (sensitivity 24%, 95% confidence interval [CI] 9%-45%; specificity 100%, 95% CI 88%-100%). The assay validated here, was developed using the MOG construct provided by Dr Waters(11) and the validation was based on a blinded comparison with the Oxford assay. Comparison was also made with the Euroimmun fixed cell-based kit assay.(14) A recent longitudinal analysis with 2 year follow-up suggested that persistence of MOG-IgG is associated with relapses thus warranting relapse preventing.(10) Detection of MOG-IgG1 allows distinction from MS and is generally indicative of a relapsing disease, mandating initiation of immunosuppression, even after the first attack in some, thereby reducing attack frequency and disability in the future.

**Useful For:** Diagnosis of inflammatory demyelinating diseases (IDDs) with similar phenotype to neuromyelitis optica spectrum disorder (NMOSD), including optic neuritis (single or bilateral) and transverse myelitis Diagnosis of autoimmune myelin oligodendrocyte glycoprotein (MOG)-opathy Diagnosis of neuromyelitis optica (NMO) Distinguishing NMOSD, acute disseminated encephalomyelitis (ADEM), optic neuritis, and transverse myelitis from multiple sclerosis early in the course of disease Diagnosis of ADEM Prediction of a relapsing disease course

**Interpretation:** A positive value for aquaporin-4 (AQP4)-IgG is consistent with an autoimmune astrocytopathy/neuromyelitis optica spectrum disorder (NMOSD) and justifies initiation of appropriate immunosuppressive therapy at the earliest possible time. This allows early initiation and maintenance of optimal therapy. Recommend follow-up in 3 to 6 months if NMOSD is suspected. A positive value for myelin oligodendrocyte glycoprotein (MOG)-IgG is consistent with an neuromyelitis optica (NMO)-like phenotype, and in the setting of acute disseminated encephalomyelitis (ADEM), optic neuritis (ON) and transverse myelitis (TM) indicates an autoimmune oligodendrogliopathy with potential for relapsing course. Identification of MOG-IgG allows distinction from multiple sclerosis (MS) and may justify initiation of appropriate immunosuppressive therapy (not MS disease-modifying agents) at the earliest possible time. This allows early initiation and maintenance of optimal therapy. Recommend follow-up in 3 to 6 months as persistence of MOG-IgG seropositivity predicts a relapsing course. Detection of both antibodies is rare and unusual. AQP4-IgG and MOG-IgG are not found in MS or healthy subjects.

**Reference Values:**

MOG FACS, S  
Negative  
Reference values apply to all ages.

NMO/AQP4 FACS, S  
Negative  
Reference values apply to all ages.


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**F2**

**Coagulation Factor II Activity Assay, Plasma**

**Clinical Information:** Factor II (prothrombin) is a vitamin K-dependent serine protease synthesized in liver. It participates in the final common pathway of coagulation, as the substrate for the prothrombinase enzyme complex. Prothrombin is the precursor of thrombin (IIa) which converts fibrinogen to fibrin. Plasma biological half-life is about 3 days. Deficiency of factor II may cause prolonged prothrombin time and activated partial thromboplastin time. Deficiency may result in a bleeding diathesis.

**Useful For:** Diagnosing a congenital deficiency (rare) of coagulation factor II Evaluating acquired deficiencies associated with liver disease or vitamin K deficiency, oral anticoagulant therapy, and antibody-induced deficiencies (eg, in association with lupus-like anticoagulant) Determining warfarin treatment stabilization in patients with nonspecific inhibitors (ie, lupus anticoagulant) Determining degree of anticoagulation with warfarin to correlate with level of protein S Investigation of prolonged prothrombin time or activated partial thromboplastin time

**Interpretation:** Liver disease, vitamin K deficiency, or warfarin anticoagulation can cause decreased factor II activity. Homozygotes generally have levels of <25% Heterozygotes generally have levels of <50% Normal newborn infants may have levels of 25% to 50%

**Reference Values:**

Adults: 75-145%
Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =25%) which may remain below adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.


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**F2IS**

**Coagulation Factor II Inhibitor Screen, Plasma**

**Clinical Information:** Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy, or can occur spontaneously without known cause or in response to a variety of medical conditions including the postpartum state, immunologic disorders, certain antibiotic therapies, some malignancies, and old age. Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

**Useful For:** Detection and quantitation of inhibitor to factor II This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor or other inhibitors that are not specific for coagulation factors. This test is not useful for the detection of a nonspecific circulating anticoagulant.
**Interpretation:** Normally, there is no inhibitor, i.e., negative. If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

**Reference Values:**

**FACTOR II ACTIVITY ASSAY**

Adults: 75-145%

Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =25%) which may remain below adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

**FACTOR II INHIBITOR SCREEN**

Negative

**Clinical References:**


**Coagulation Factor IX Activity Assay, Plasma**

**Clinical Information:** Factor IX is a vitamin K-dependent serine protease synthesized in the liver and participates in the intrinsic coagulation pathway. Its biological half-life is 18 to 24 hours. Congenital deficiency inherited as an X-linked recessive bleeding disorder (hemophilia B). Severe deficiency (<1%) characterized by hemarthroses, deep tissue bleeding, excessive bleeding with trauma and ecchymoses. Acquired deficiency associated with liver disease, vitamin K deficiency, warfarin therapy and inhibitors (rare).

**Useful For:** Diagnosing deficiencies, particularly hemophilia B (Christmas disease) Assessing the impact of liver disease on hemostasis Investigation of a prolonged activated partial thromboplastin time

**Interpretation:** Acquired deficiency is more common than congenital. Mild hemophilia B: 5% to 50% Moderate hemophilia B: 1% to 5% Severe hemophilia B: <1%

**Reference Values:**

Adults: 65-140%

Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =20%) which may not reach adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

**Clinical References:**


**Coagulation Factor V Activity Assay, Plasma**

**Clinical Information:** Factor V is a vitamin K-independent protein synthesized in the liver and in other tissues (endothelium, megakaryocytes/platelets). In its thrombin-activated form (factor Va), it serves as an essential cofactor in the prothrombinase enzyme complex which converts prothrombin to thrombin (the prothrombinase complex consists of the enzyme, activated factor X, factor Va cofactor, a phospholipid surface, and calcium). Deficiency of factor V may cause prolonged prothrombin time and activated partial thromboplastin time. Deficiency may result in a bleeding diathesis. Plasma biological half-life varies from 12 to 36 hours. Platelets contain 20% to 25% of the factor V in blood. Factor V (also known as labile factor) is highly susceptible to proteolytic inactivation, with the potential for spuriously decreased assay results.
**Useful For:** Diagnosing congenital deficiencies (rare) of coagulation factor V Evaluating acquired deficiencies associated with liver disease, factor V inhibitors, myeloproliferative disorders, and intravascular coagulation and fibrinolysis Investigation of prolonged prothrombin time or activated partial thromboplastin time

**Interpretation:** See Cautions Acquired deficiencies are much more common than congenital (see Useful For). Congenitally deficient homozygotes generally have levels ≤10% to 20%. Congenitally deficient heterozygotes generally have levels ≤50%. Congenital deficiency may occur in combined association with factor VIII deficiency.

**Reference Values:**

- Adults: 70-165%
- Normal, full-term newborn infants may have borderline low or mildly decreased levels (> or =30% to 35%) which reach adult levels within 21 days postnatal. Healthy premature infants (30-36 weeks gestation) may have borderline low or mildly decreased levels.*
- *See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

**Clinical References:**


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**Coagulation Factor V Inhibitor Screen, Plasma**

**Clinical Information:** Factor V inhibitors can occur in patients with congenital factor V deficiency after transfusion of fresh frozen plasma, however, more commonly, they occur spontaneously in previously healthy older patients who have no underlying diseases. Topical bovine thrombin or fibrin glue, which contain bovine thrombin and factor V, are commonly used in surgery for topical hemostasis, can result in development of anti-bovine thrombin/factor V inhibitors that cross-react with human thrombin and factor V. Other associations include antibiotics, transfusions and malignancies.

**Useful For:** Detection and quantitation of inhibitors against coagulation factor V This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor or other inhibitors that are not specific for coagulation factors. This test is not useful for the detection of a nonspecific circulating anticoagulant.

**Interpretation:** Normally, there is no inhibitor, ie, negative. If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

**Reference Values:**

**FACTOR V ACTIVITY ASSAY**

- Adults: 75-165%
- Normal, full-term newborn infants may have borderline low or mildly decreased levels (> or =30-35%) which reach adult levels within 21 days postnatal.*
- *See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

**FACTOR V INHIBITOR SCREEN**

- Negative

**Clinical References:**

Coagulation Factor VII Activity Assay, Plasma

Clinical Information: Factor VII is a vitamin K-dependent serine protease synthesized in the liver. It is a component of the extrinsic coagulation scheme, measured by the prothrombin time. Plasma biological half-life is about 3 to 6 hours. Deficiency may result in a bleeding diathesis.

Useful For: Diagnosing congenital deficiency of coagulation factor VII Evaluating acquired deficiencies associated with liver disease, oral anticoagulant therapy, and vitamin K deficiency Determining degree of anticoagulation with warfarin to correlate with level of protein C Investigation of a prolonged prothrombin time

Interpretation: Liver disease, vitamin K deficiency, or warfarin anticoagulation can cause decreased factor VII activity. Heterozygotes generally have levels of < or =50%. Homozygotes have levels usually <20%. Newborn infants usually have levels > or =25%.

Reference Values:
Adults: 65-180%

Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =20%) which increase within the first postnatal week but may not reach adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.


Coagulation Factor VII Inhibitor Screen, Plasma

Clinical Information: Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy, or can occur spontaneously without known cause or in response to a variety of medical conditions including the postpartum state, immunologic disorders, certain antibiotic therapies, some malignancies, and old age. Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

Useful For: Detection and quantitation of inhibitor to coagulation factor VII This test is not useful for the detection of a lupus-like circulating anticoagulant inhibitor or other inhibitors that are not specific for coagulation factors. This test is not useful for the detection of a nonspecific circulating anticoagulant.

Interpretation: Normally, there is no inhibitor, ie, negative. If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

Reference Values:
FACTOR VII ACTIVITY ASSAY
Adults: 65-180%

Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =20%), which increase within the first postnatal week but may not reach adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

FACTOR VII INHIBITOR SCREEN
Negative

Coagulation Factor VIII Activity Assay, Plasma

Clinical Information: Factor VIII is synthesized in the liver, and perhaps in other tissues. It is a coagulation cofactor which circulates bound to von Willebrand factor and is part of the intrinsic coagulation pathway. The biological half-life is 9 to 18 hours (average is 12 hours). Congenital factor VIII decrease is the cause of hemophilia A which has an incidence of 1 in 10,000 and is inherited in a recessive sex-linked manner on the X chromosome. Severe deficiency (<1%) characteristically demonstrates as hemarthrosis, deep-tissue bleeding, excessive bleeding with trauma and ecchymoses. Factor VIII may be decreased in von Willebrand disease. Acquired deficiency states also occur. Antibodies specific for factor VIII are the most commonly occurring specific inhibitors of coagulation factors and can produce serious bleeding disorders (acquired hemophilia). Factor VIII is highly susceptible to proteolytic inactivation, with the potential for spuriously decreased assay results.

Useful For: Diagnosing hemophilia A Diagnosing von Willebrand disease when measured with the von Willebrand factor (VWF) antigen and VWF activity Diagnosing acquired deficiency states Investigation of prolonged activated partial thromboplastin time

Interpretation: See Cautions. Mild hemophilia A: 5% to 50% Moderate hemophilia A: 1% to 5% Severe hemophilia A: <1% Congenital deficiency may also occur in combined association with factor V deficiency. Liver disease usually causes an increase of factor VIII activity. Acquired deficiencies of factor VIII have been associated with myeloproliferative or lymphoproliferative disorders (acquired von Willebrand disease; VWD), inhibitors of factor VIII (autoantibodies, post-partum conditions, etc.), and intravascular coagulation and fibrinolysis. May be decreased with von Willebrand factor in VWD

Reference Values: Adults: 55-200% Normal, full-term newborn infants or healthy premature infants usually have normal or elevated factor VIII.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.


Coagulation Factor VIII Inhibitor Screen, Plasma

Clinical Information: Useful for detecting the presence and titer of a specific factor inhibitor directed against coagulation factor VIII. These inhibitors are antibodies that are found most often in response to the use of factor VIII concentrate by patients congenitally deficient in factor VIII (hemophilia A). Factor VIII inhibitors can also develop in non-hemophiliac patients (not previously factor VIII deficient), most commonly in the following situations: 1) in the elderly; 2) in postpartum patients; and 3) in patients with autoimmune illness. Testing will include coagulation factor VIII activity assay with dilutions to evaluate assay inhibition, and if the factor VIII assay activity is decreased, an inhibitor screen to look for specific factor VIII inhibition. If specific inhibition is apparent, it will be titered. Note: If type of inhibitor is unknown, see Coagulation Consultation, Lupus-Like Anticoagulant/Circulating Anticoagulant, Plasma.

Reference Values: Negative If positive, quantitated in Bethesda units.
Coagulation Factor X Activity Assay, Plasma

**Clinical Information:** Factor X is a vitamin K-dependent serine protease that is synthesized in the liver. Its biological half-life is 24 to 48 hours. Factor X participates in both intrinsic and extrinsic pathways of coagulation (final common pathway) by serving as the enzyme (factor Xa) in the prothrombinase complex. Congenital factor X deficiency is rare. Acquired deficiency associated with liver disease, warfarin therapy, vitamin K deficiency, systemic amyloidosis and inhibitors (rare). Deficiency may cause prolonged prothrombin time and activated partial thromboplastin time.

**Useful For:** Diagnosing deficiency of coagulation factor X, congenital or acquired Evaluating hemostatic function in liver disease Investigation of prolonged prothrombin time or activated partial thromboplastin time

**Interpretation:** Acquired deficiency more common than congenital Homozygotes: <25%
Heterozygotes: 25% to 50%

**Reference Values:**
Adults: 70-150%
Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =15-20%) which may not reach adult levels for > or =180 days postnatal.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

**Clinical References:**

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Coagulation Factor X Chromogenic Activity Assay, Plasma

**Clinical Information:** The antithrombotic effect of oral vitamin K antagonists (eg, warfarin) is mediated by reduction in the plasma activity of vitamin K-dependent procoagulant factors II (prothrombin) and X. The intensity of oral anticoagulation therapy with vitamin K antagonists must be monitored and adjusted to a narrow therapeutic range; undermedicating increases the risk of thrombosis, while overmedicating increases the risk of bleeding. Such therapy typically is monitored with the prothrombin time/international normalized ratio (INR) system. Lupus anticoagulants (LAC) are autoantibodies that interfere with phospholipid-dependent clotting tests and most commonly cause prolongation of the activated partial thromboplastin time (APTT). LAC can be associated with a prothrombotic disorder termed the antiphospholipid syndrome. LAC occasionally may cause prolongation of the baseline prothrombin time, rendering the INR system inaccurate for monitoring the intensity of oral anticoagulant therapy. LAC-induced prolongation of the prothrombin time is most commonly seen with recombinant human tissue factor thromboplastins (ie, prothrombin time reagents) with a low international sensitivity index (ISI) such as Innovin or RecombiPlasTin 2G (ISI = 1.0). The chromogenic factor X activity is an alternative assay for monitoring oral anticoagulant therapy. This assay is unaffected by LAC because the assay end point is not a phospholipid-dependent clotting time. Argatroban is a parenteral direct thrombin inhibitor that is approved for treatment of heparin-induced thrombocytopenia (HIT), an antibody-mediated prothrombotic disorder. Argatroban therapy prolongs the prothrombin time, which also renders the INR inaccurate for monitoring the warfarin effect while transitioning from Argatroban to oral anticoagulant therapy. The chromogenic coagulation factor X activity assay may be used as an alternative to the INR for monitoring and adjusting the warfarin dose during this transition.

**Useful For:** Monitoring warfarin anticoagulant therapy, especially in patients whose plasma contains lupus anticoagulants that interfere with baseline prothrombin time/international normalized ratio and in patients receiving the drug Argatroban who are being transitioned to warfarin
**Interpretation:** A chromogenic factor X activity of approximately 20% to 40% corresponds to the usual warfarin international normalized ratio range (ie, 2.0-3.0).

**Reference Values:**

> or =18 years of age: 60%-140%

   Chromogenic Factor X activity generally correlates with the one-stage factor X activity. In full term or premature neonates, infants, and children, the one-stage factor X activity* is lower than adult reference range and progressively rises to the adult reference range by adolescence. However, no similar data for the chromogenic factor X activity have been published.

   *See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

**Clinical References:**


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**Coagulation Factor X Inhibitor Screen, Plasma**

**Clinical Information:** Coagulation factor inhibitors arise in patients who are congenitally deficient in a specific factor in response to factor replacement therapy, or can occur spontaneously without known cause or in response to a variety of medical conditions including the postpartum state, immunologic disorders, certain antibiotic therapies, some malignancies, and old age. Inhibitors of factor VIII coagulant activity are the most commonly occurring of the specific factor inhibitors.

**Useful For:** Detection and quantitation of inhibitor to coagulation factor X This test is not useful for detecting presence of inhibitors directed against other clotting factors and is not useful for the detection of a nonspecific circulating anticoagulant. This test is not useful for the detection of lupus anticoagulants.

**Interpretation:** Normally, there is no inhibitor, ie, negative. If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

**Reference Values:**

**FACTOR X ACTIVITY ASSAY**

   Adults: 70-150%

   Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =15-20%) which may not reach adult levels for > or =180 days postnatal.*

   *See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

**FACTOR X INHIBITOR SCREEN**

   Negative

**Clinical References:**


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**Coagulation Factor XI Activity Assay, Plasma**

**Clinical Information:** Factor XI is synthesized in the liver. Its biological half-life is 60 to 80 hours. Factor XI is a component of intrinsic coagulation pathway which, when activated, activates factor IX to IXa. Factor XI deficiency may cause prolonged partial thromboplastin time. Deficiency associated with mild bleeding diathesis, but there is poor correlation between activity level and clinical bleeding. A relatively high incidence of congenital deficiency occurs among Ashkenazi Jewish descent (hemophilia
Useful For: Diagnosing deficiency of coagulation factor XI. Investigation of prolonged activated partial thromboplastin time

Interpretation: Acquired deficiency is associated with liver disease and rarely inhibitors. Homozygotes: <20%. Heterozygotes: 20% to 60%

Reference Values:
Adults: 55-150%

Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =10%) which may not reach adult levels for > or =180 days postnatal.* *See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.


### Coagulation Factor XI Inhibitor Screen, Plasma

**Clinical Information:** Factor XI inhibitors typically arise in patients with congenital XI deficiency (hemophilia C), after infusion of fresh frozen plasma or factor XI concentrates. Acquired factor XI inhibitors rarely occur spontaneously.

**Useful For:** Detection and quantitation of inhibitor to coagulation factor XI. This test is not useful for detecting presence of inhibitors directed against other clotting factors and is not useful for the detection of a nonspecific circulating anticoagulant. This test is not useful for the detection of lupus anticoagulants.

**Interpretation:** Normally, there is no inhibitor, ie, negative. If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

**Reference Values:**

**FACTOR XI ACTIVITY ASSAY**
Adults: 55-150%

Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =10%) which may not reach adult levels for > or =180 days postnatal.* *See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

**FACTOR XI INHIBITOR SCREEN**
Negative


### Coagulation Factor XII Activity Assay, Plasma

**Clinical Information:** Factor XII is synthesized in the liver. Its biological half-life is 40 to 50 hours. Factor XII is a component of the contact activation system and is involved in both intrinsic pathway and fibrinolytic system. Factor XII deficiency is often discovered when activated partial thromboplastin time is found to be unexpectedly long. The deficiency causes no known bleeding disorder. An association between severe factor XII deficiency and thrombosis risk has been proposed.
but not proven.

**Useful For:** Diagnosing deficiency of coagulation factor XII Determining cause of prolonged activated partial thromboplastin time

**Interpretation:** Acquired deficiency is associated with liver disease, nephritic syndrome, and chronic granulocytic leukemia. Congenital homozygous deficiency: 20% Congenital heterozygous deficiency: 20% to 50%

**Reference Values:**
Adults: 55-180%
Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =15% to 20%) which may not reach adult levels for > or =180 days postnatal.*
*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

**Clinical References:** Renne T, Schmaier AH, Nickel KF, et al: In vivo roles of factor XII. Blood 2012 Nov 22;120(22):4296-4303

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**Cobalt, 24 Hour, Urine**

**Clinical Information:** Cobalt is rare but widely distributed in the environment. It is an essential cofactor in vitamin B12. While cobalt is an essential element, cobalt deficiency has not been reported in humans. Cobalt is used in the manufacture of hard alloys with high melting points and resistance to oxidation. Cobalt salts are also used in the glass and pigment industry. Previously, cobalt salts were sometimes used as foam stabilizers in the brewing industry; this practice was banned due to the cardiovascular diseases it induced. The radioactive isotope of cobalt, (60)Co, is used as a gamma emitter in experimental biology, cancer therapy, and industrial radiography. Cobalt is not highly toxic, but large doses will produce adverse clinical manifestations. Acute symptoms are pulmonary edema, allergy, nausea, vomiting, hemorrhage, and renal failure. Chronic symptoms include pulmonary syndrome, skin disorders, and thyroid abnormalities. The inhalation of dust during machining of cobalt alloyed metals can lead to interstitial lung disease. Improperly handled (60)Co can cause radiation poisoning from exposure to gamma radiation. Urine cobalt concentrations are likely to be increased above the reference value in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. Prosthetic devices produced by DePuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Detecting cobalt exposure Monitoring metallic prosthetic implant wear

**Interpretation:** Concentrations > or =2.0 mcg/specimen indicate excess exposure. There are no Occupational Safety and Health Administration (OSHA) blood or urine criteria for occupational exposure to cobalt. Prosthesis wear is known to result in increased circulating concentration of metal ions. In a patient with a cobalt-based implant, modest increase (2-4 mcg/specimen) in urine cobalt concentration is likely to be associated with a prosthetic device in good condition. Excessive exposure is indicated when urine cobalt concentration is >5 mcg/specimen, consistent with prosthesis wear. Urine concentrations >20 mcg/specimen in a patient with a cobalt-based implant suggest significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

**Reference Values:**
0.0-1.9 mcg/specimen
Reference values apply to all ages.

Cobalt, Blood

Clinical Information: Cobalt is a naturally occurring, hard, grey element widely distributed in the environment. It is used to produce alloys in the manufacturing of aircraft engines, cutting tools, and some artificial hip and knee joint prosthesis devices. Cobalt salts are also used in the glass and pigment industry. Previously, cobalt salts were sometimes used as foam stabilizers in the brewing industry; this practice was banned due to the cardiovascular diseases it induced. One of the radioactive isotopes of cobalt, (60)Co, is used to sterilize medical equipment, in radiation therapy for cancer patients, and to irradiate food. Cobalt is an essential cofactor in vitamin B12, which is necessary for neurological function, brain function, and the formation of blood. For most people, food is the largest source of cobalt intake. However, more than a million workers are potentially exposed to cobalt and its compounds, with the greatest exposure in mining processes, cemented tungsten-carbide industry, cobalt powder industry, and alloy production industry. Cobalt is not highly toxic, but large doses will produce adverse clinical manifestations. Acute symptoms include pulmonary edema, allergy, nausea, vomiting, hemorrhage, and renal failure. Chronic exposure to cobalt-containing hard metal (dust or fume) can result in a serious lung disease called “hard metal lung disease,” which is a type of pneumoconiosis (lung fibrosis). Furthermore, inhalation of cobalt particles can cause respiratory sensitization, asthma, shortness of breath, and decreased pulmonary function. Even though the primary route of occupational exposure to cobalt is the respiratory tract, skin contact is also important because dermal exposures to hard metal and cobalt salts can result in significant systemic uptake. Sustained exposures can cause skin sensitization, which may result in eruptions of contact dermatitis. Per FDA recommendations, orthopedic surgeons should consider measuring and following serial cobalt concentrations in EDTA anti-coagulated whole blood in symptomatic patients with metal-on-metal hip implants as part of their overall clinical evaluation. Blood cobalt concentrations are likely to be increased above the reference range in patients with joint prosthesis containing cobalt. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside are typically made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Monitor exposure to cobalt Monitoring metallic prosthetic implant wear

Interpretation: Concentrations greater or equal to 1.0 ng/mL indicate possible environmental or occupational exposure. Cobalt concentrations associated with toxicity must be interpreted in the context of the source of exposure. In the context of failed metal-on-metal prosthetics, elevated cobalt in serum or blood is rarely the initial finding and is often preceded by physical symptoms including: reduced range of motion, swelling, inflammation around the joints, and general discomfort or pain. The ACGIH Biological Exposure Index (BEI) for cobalt in blood is 1 mcg/L (1 ng/mL), which should be collected at the end of shift at the end of the work week.

Reference Values:
0-17 years: not established
> or =18 years: <1.0 ng/mL

Cobalt, Random, Urine

Clinical Information: Cobalt is rare but widely distributed in the environment. It is an essential cofactor in vitamin B12. While cobalt is an essential element, cobalt deficiency has not been reported in humans. Cobalt is used in the manufacture of hard alloys with high melting points and resistance to oxidation. Cobalt salts are also used in the glass and pigment industry. Previously, cobalt salts were sometimes used as foam stabilizers in the brewing industry; this practice was banned due to the cardiovascular diseases it induced. The radioactive isotope of cobalt, (60)Co, is used as a gamma emitter in experimental biology, cancer therapy, and industrial radiography. Cobalt is not highly toxic, but large doses will produce adverse clinical manifestations. Acute symptoms are pulmonary edema, allergy, nausea, vomiting, hemorrhage, and renal failure. Chronic symptoms include pulmonary syndrome, skin disorders, and thyroid abnormalities. The inhalation of dust during machining of cobalt alloyed metals can lead to interstitial lung disease. Improperly handled (60)Co can cause radiation poisoning from exposure to gamma radiation. Urine cobalt concentrations are likely to be increased above the reference value in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Detecting cobalt exposure Monitoring metallic prosthetic implant wear

Interpretation: Concentrations > or = 2.0 mcg/L indicate excess exposure. There are no Occupational Safety and Health Administration (OSHA) blood or urine criteria for occupational exposure to cobalt. Prosthesis wear is known to result in increased circulating concentration of metal ions. In a patient with a cobalt-based implant, modest increase (2-4 mcg/L) in urine cobalt concentration is likely to be associated with a prosthetic device in good condition. Excessive exposure is indicated when urine cobalt concentration is >5 mcg/L, consistent with prosthesis wear. Urine concentrations >20 mcg/L in a patient with a cobalt-based implant suggest significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

Reference Values:
0.0-1.9 mcg/L
Reference values apply to all ages.


Cobalt, Serum

Clinical Information: Cobalt is rare but widely distributed in the environment, used in the manufacture of hard alloys with high melting points and resistance to oxidation; cobalt alloys are used in manufacture of some artificial joint prosthesis devices. Cobalt salts are used in the glass and pigment industry. Previously, cobalt salts were sometimes used as foam stabilizers in the brewing industry; this practice was banned due to the cardiovascular diseases it induced. The radioactive isotope of cobalt, (60)Co, is used as a gamma emitter in experimental biology, cancer therapy, and industrial radiography.
Cobalt is an essential cofactor in vitamin B12 metabolism. Cobalt deficiency has not been reported in humans. Cobalt is not highly toxic, but large doses will produce adverse clinical manifestations. Acute symptoms are pulmonary edema, allergy, nausea, vomiting, hemorrhage, and renal failure. Chronic symptoms include pulmonary syndrome, skin disorders, and thyroid abnormalities. The inhalation of dust during machining of cobalt alloyed metals can lead to interstitial lung disease. Serum cobalt concentrations are likely to be increased above the reference range in patients with joint prosthesis containing cobalt. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside are typically made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Detecting cobalt toxicity Monitoring metallic prosthetic implant wear

**Interpretation:** Concentrations greater than or equal to 1.0 ng/mL indicate possible environmental or occupational exposure. Cobalt concentrations associated with toxicity must be interpreted in the context of the source of exposure. If cobalt is ingested, concentrations greater than 5 ng/mL suggest major exposure and likely toxicity. If cobalt exposure is due to orthopedic implant wear, there are no large case number reports associating high circulating serum cobalt with toxicity. There are no Occupational Health and Safety Administration (OSHA) blood or urine criteria for occupational exposure to cobalt. Prosthesis wear is known to result in increased circulating concentration of metal ions. Modest increase (4-10 ng/mL) in serum cobalt concentration is likely to be associated with a prosthetic device in good condition. Serum concentrations above 10 ng/mL in a patient with cobalt-based implant suggest significant prosthetic wear. Increased serum trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure. However, the FDA recommends testing cobalt in EDTA anticoagulated whole blood in symptomatic patients with metal-on-metal implants.

**Reference Values:**
0.0-0.9 ng/mL  
<10 ng/mL (MoM implant)  
Reference values apply to all ages.

The reported unit of measurement for cobalt of ng/mL is equivalent to mcg/L.

**Clinical References:**

**COBCU 60353**

Cobalt/Creatinine Ratio, Random, Urine

**Clinical Information:** Cobalt is rare but widely distributed in the environment. It is an essential cofactor in vitamin B12. While cobalt is an essential element, cobalt deficiency has not been reported in humans. Cobalt is used in the manufacture of hard alloys with high melting points and resistance to oxidation. Cobalt salts are also used in the glass and pigment industry. Previously, cobalt salts were sometimes used as foam stabilizers in the brewing industry; this practice was banned due to the cardiovascular diseases it induced. The radioactive isotope of cobalt, (60)Co, is used as a gamma emitter in experimental biology, cancer therapy, and industrial radiography. Cobalt is not highly toxic, but large doses will produce adverse clinical manifestations. Acute symptoms are pulmonary edema, allergy, nausea, vomiting, hemorrhage, and renal failure. Chronic symptoms include pulmonary syndrome, skin disorders, and thyroid abnormalities. The inhalation of dust during machining of cobalt alloyed metals can lead to interstitial lung disease. Improperly handled (60)Co can cause radiation poisoning from exposure to gamma radiation. Cobalt concentrations are likely to be increased above the reference value in patients with metallic joint prosthesis. Prosthetic devices produced by
Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. Prosthetic devices produced by DePuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Detecting cobalt exposure Monitoring metallic prosthetic implant wear

**Interpretation:** Concentrations > or = 2.0 mcg/g creatinine indicate excess exposure. There are no Occupational Safety and Health Administration (OSHA) blood or urine criteria for occupational exposure to cobalt. Prosthesis wear is known to result in increased circulating concentration of metal ions. In a patient with a cobalt-based implant, modest increase (2-4 mcg/g creatinine) in urine cobalt concentration is likely to be associated with a prosthetic device in good condition. Excessive exposure is indicated when urine cobalt concentration is >5 mcg/g creatinine, consistent with prosthesis wear. Urine concentrations >20 mcg/g creatinine in a patient with a cobalt-based implant suggest significant prosthesis wear. Increased urine trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

**Reference Values:**
0.0-1.9 mcg/g Creatinine
Reference values apply to all ages.

**Clinical References:**

**FCOKE 75174**

**Cocaine Analysis - Whole Blood**

**Reference Values:**

**Cocaine Screen:**
Cocaine and Metabolite, UA â€“ Negative; Cutoff: 25 ng/mL

**Cocaine Confirmation:** Cocaine
Benzoylcegonine
Confirmation threshold: 10 ng/mL

**COKMX 62720**

**Cocaine and Metabolite Confirmation, Chain of Custody, Meconium**

**Clinical Information:** Cocaine is an alkaloid found in Erythroxylon coca, which grows principally in the northern South American Andes and to a lesser extent in India, Africa, and Java.(1) Cocaine is a powerfully addictive stimulant drug. Cocaine abuse has a long history and is rooted into the drug culture in the United States,(2) and is one of the most common illicit drugs of abuse.(3,4) Cocaine is rapidly metabolized primarily to benzoylecgonine, which is further metabolized to m-hydroxybenzoylecgonine (m-HOBE).(1,5) Cocaine is frequently used with other drugs, most commonly ethanol, and the simultaneous use of both drugs can be determined by the presence of the unique metabolite cocaethylene.(4) Intrauterine drug exposure to cocaine has been associated with placental abruption, premature labor, small for gestational age status, microcephaly, and congenital anomalies (eg, cardiac and genitourinary abnormalities, necrotizing enterocolitis, and central nervous system stroke or hemorrhage).(6) The disposition of drug in meconium, the first fecal material passed by the neonate, is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing of amniotic
fluid.(7) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation.(8) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(7) Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection of in utero drug exposure up to 5 months before birth. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

**Interpretation:** The presence of any of the following: cocaine, benzoylecgonine, cocaethylene, or m-hydroxybenzoylecgonine, at > or =50 ng/g is indicative of in utero drug exposure up to 5 months before birth.

**Reference Values:**

- **Negative**
  - Positives are reported with a quantitative LC-MS/MS result.
  - Cutoff concentrations
    - Cocaine by LC-MS/MS: 50 ng/g
    - Benzoylecgonine by LC-MS/MS: 50 ng/g
    - Cocaethylene by LC-MS/MS: 50 ng/g
    - m-Hydroxybenzoylecgonine by LC-MS/MS: 50 ng/g

**Clinical References:**


**Useful For:** Detecting and confirming drug abuse involving cocaine. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen confirmation is minimized.
tampering would be limited.

**Interpretation:** Reports will specifically indicate the presence or absence of cocaine and benzoylecgonine. The presence of cocaine, or its major metabolite, benzoylecgonine, indicates use within the past 4 days. Cocaine has a 6-hour half-life, so it will be present in urine for 1 day after last use. Benzoylecgonine has a half-life of 12 hours, so it will be detected in urine up to 4 days after last use. There is no correlation between concentration and pharmacologic or toxic effects.

**Reference Values:**

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<th>Suspect</th>
<th>Confirm</th>
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<td><strong>Cutoff concentrations:</strong></td>
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<tr>
<td>IMMUNOASSAY SCREEN</td>
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**Clinical References:**

Cocaine and Metabolites Confirmation, Meconium

Clinical Information: Cocaine is an alkaloid found in Erythroxylon coca, which grows principally in the northern South American Andes and to a lesser extent in India, Africa, and Java.(1) Cocaine is a powerfully addictive stimulant drug. Cocaine abuse has a long history and is rooted into the drug culture in the United States,(2) and is 1 of the most common illicit drugs of abuse.(3,4) Cocaine is rapidly metabolized primarily to benzoylecgonine, which is further metabolized to m-hydroxybenzoylecgonine (m-HOBE).(1,5) Cocaine is frequently used with other drugs, most commonly ethanol, and the simultaneous use of both drugs can be determined by the presence of the unique metabolite cocaethylene.(4) Intrauterine drug exposure to cocaine has been associated with placental abruption, premature labor, small for gestational age status, microcephaly, and congenital anomalies (eg, cardiac and genitourinary abnormalities, necrotizing enterocolitis, and central nervous system stroke or hemorrhage).(6) The disposition of drug in meconium, the first fecal material passed by the neonate, is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing of amniotic fluid.(7) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation.(8) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(7)

Useful For: Detection of in utero drug exposure up to 5 months before birth

Interpretation: The presence of any of the following: cocaine, benzoylecgonine, cocaethylene, or m-hydroxybenzoylecgonine, at 50 ng/g or more is indicative of in utero drug exposure up to 5 months before birth.

Reference Values:
Negative
Positives are reported with a quantitative LC-MS/MS result.
Cutoff concentrations
Cocaine by LC-MS/MS: 50 ng/g
Benzoylecgonine by LC-MS/MS: 50 ng/g
Cocaethylene by LC-MS/MS: 50 ng/g
m-Hydroxybenzoylecgonine by LC-MS/MS: 50 ng/g


Coccidioides Antibody with Reflex, Serum

Clinical Information: Coccidioidomycosis (Valley fever, San Joaquin Valley fever, Desert Rheumatism) is caused by the dimorphic fungus Coccidioides immitis/posadasii, which is found in the southwestern United States and in Central and South America. It is acquired by inhalation of airborne Coccidioides arthroconidia. The majority of infections are subclinical. Among symptomatic patients, the majority will present acute flulike, pulmonary symptoms approximately 7 to 28 days post exposure,
which may include chest pain, cough, fever, malaise, and lymphadenopathy. A rash often develops within a couple of days, followed by erythema nodosum or multiforme with accompanying arthralgia. A pulmonary coin-like lesion or nodule may develop months following infection and may be a source of infection if the patient becomes immunosuppressed in the future. Coccidioidomycosis may disseminate beyond the lungs to involve multiple organs including the meninges. Individuals at greater risk for dissemination include African-Americans, patients of Filipino descent, pregnant women, and immunocompromised patients. Serologic testing for coccidioidomycosis should be considered when patients exhibit symptoms of pulmonary or meningeal infection and have lived or traveled in areas where Coccidioides immitis/posadasii is endemic. Any history of exposure to the organism or travel cannot be overemphasized when a diagnosis of coccidioidomycosis is being considered.

**Useful For:** Screening for detection of antibodies to Coccidioides immitis/posadasii

**Interpretation:** A positive result is presumptive evidence that the patient was previously or is currently infected with Coccidioides immitis/posadasii. This specimen will be tested by complement fixation and immunodiffusion for confirmation. A negative result indicates the absence of antibodies to Coccidioides immitis/posadasii and is presumptive evidence that the patient has not been previously exposed to and is not infected with Coccidioides. However, a negative result does not preclude the diagnosis of coccidioidomycosis as the specimen may have been drawn before antibodies levels were detectable due to early acute infection or immunosuppression. If infection is suspected, another specimen should be drawn in 7 to 14 days and retested to look for seroconversion. This test is designed for the qualitative detection of both IgM- and IgG-class antibodies against antigens from Coccidioides. The report will not indicate which class of antibody is present.

**Reference Values:**
Negative

**Clinical References:**

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**Coccidioides Antibody, Complement Fixation and Immunodiffusion, Serum**

**Reference Values:**
Negative

---

**Coccidioides Antibody, Serum**

**Clinical Information:** Coccidioidomycosis (Valley fever, San Joaquin Valley fever) is a fungal infection found in the southwestern United States, Central America, and South America. It is acquired by inhalation of arthroconidia of Coccidioides immitis. Usually, it is a mild, self-limiting pulmonary infection, often leaving a coin-like lesion. Less commonly, chronic pneumonia may persist or progress to fibronodular, cavitary disease. A rash often develops within a day or 2, followed by erythema nodosum or multiforme and accompanying arthralgias. About 2 weeks after exposure, symptomatic patients develop fever, cough, malaise, and anorexia; chest pain is often severe. Coccidioidomycosis may disseminate beyond the lungs to involve multiple organs including the meninges. IgG antibody is detected by the complement-fixation tests. Precipitating antibodies (IgM and IgG) are detected by immunodiffusion. They are rarely found in cerebrospinal fluid; however, their presence is associated with meningitis. Chronic coccidioidal pulmonary cavities are often accompanied by IgG and IgM precipitating antibodies. Serologic testing for coccidioidomycosis should be considered when patients exhibit symptoms of pulmonary or meningeal infection and have lived or traveled in areas where Coccidioides immitis is endemic. Any history of exposure to the organism or travel cannot be overemphasized when a diagnosis of coccidioidomycosis is being considered.

**Useful For:** Diagnosing coccidioidomycosis in serum specimens
Interpretation: Complement Fixation (CF): Titers of 1:2 or higher may suggest active disease; however, titers may persist for months after infection has resolved. Increasing CF titers in serial specimens are diagnostic of active disease. Immunodiffusion (ID): The presence of IgM antibody may be detectable within 2 weeks after the onset of symptoms; however, antibody may be detected longer than 6 months after infection. The presence of IgG antibody parallels the CF antibody and may suggest an active or a recent asymptomatic infection with Coccidioides immitis; however, antibody may persist after the infection has resolved. An equivocal result (a band of nonidentity) cannot be interpreted as significant for a specific diagnosis. However, this may be an indication that a patient should be followed serologically. Over 90% of primary symptomatic cases will be detected by combined ID and CF testing.

Reference Values:
COMPLEMENT FIXATION
Negative
If positive, results are titered.

IMMUNODIFFUSION
Negative
Results are reported as positive, negative, or equivocal.


Coccidioides Antibody, Spinal Fluid

Clinical Information: Coccidioidomycosis (valley fever, San Joaquin Valley fever) is a fungal infection found in the southwestern United States, Central America, and South America. It is acquired by inhalation of arthroconidia of Coccidioides immitis. Usually, it is a mild, self-limiting pulmonary infection, often leaving a coin-like lesion. Less commonly, chronic pneumonia may persist or progress to fibronodular cavitary disease. A rash often develops within 1 to 2 days, followed by erythema nodosum or multiforme and accompanying arthralgias. About 2 weeks after exposure, symptomatic patients develop fever, cough, malaise, and anorexia; chest pain is often severe. Coccidioidomycosis may disseminate beyond the lungs to involve multiple organs including the meninges. Serologic testing for coccidioidomycosis should be considered when patients exhibit symptoms of meningeal infection and have lived or traveled in areas where Coccidioides immitis is endemic. Any history of exposure to the organism or travel cannot be overemphasized when coccidioidomycosis serologic tests are being considered.

Useful For: Diagnosing coccidioidomycosis from spinal fluid specimens Diagnosing meningitis from spinal fluid specimens

Interpretation: Complement Fixation (CF): IgG antibody is detected by CF testing. Any CF titer in cerebrospinal fluid (CSF) should be considered significant. A positive complement fixation test in unconcentrated CSF is diagnostic of meningitis. Immunodiffusion (ID): IgM and IgG precipitins are rarely found in CSF. However, when present, they are diagnostic of meningitis (100% specific). Since the ID test is 100% specific, it is helpful in interpreting CF results. Early primary antibody (IgM) found in coccidioidomycosis can be detected by the IgM-specific ID test. IgM precipitins may be detectable within 1 to 4 weeks after the onset of symptoms. The presence of IgG antibody parallels the CF antibody and indicates an active or a recent asymptomatic infection with Coccidioides immitis. Both IgG and IgM antibodies are rarely detected 6 months after infection. However, in some patients having disseminated infection, both IgG and IgM antibodies may be present for several years. IgM and IgG precipitins are not prognostic. An equivocal result (a band of nonidentity) cannot be interpreted as significant for a specific diagnosis. However, this may be an indication that a patient should be followed serologically. The sensitivity of serologic testing (CF and ID combined) for coccidioidomycosis is >90% or primary symptomatic cases.

Reference Values:
COMPLEMENT FIXATION
Coccidioides immitis/posadasii, Molecular Detection, PCR

Clinical Information: Coccidioidomycosis is caused by the dimorphic fungi, Coccidioides immitis and Coccidioides posadasii. These organisms are endemic to the southwestern regions of the United States, northern Mexico, and areas of Central and South America. The illness commonly manifests as a self-limited upper respiratory tract infection, but can also result in disseminated disease that may be refractory to treatment. (1) Clinical onset generally occurs 10 to 16 days following inhalation of coccidioidal spores (arthroconidia). (2) Disease progression may be rapid in previously healthy or immunosuppressed individuals. At present, the gold standard for the diagnosis of coccidioidomycosis is culture of the organism from clinical specimens. Culture is highly sensitive and, with the implementation of DNA probe assays for confirmatory testing of culture isolates, yields excellent specificity. (3) However, growth in culture may take up to several weeks. This often delays the diagnosis and treatment of infected individuals. In addition, the propagation of Coccidioides species in the clinical laboratory is a significant safety hazard to laboratory personnel, serving as an important cause of laboratory-acquired infections if the organism is not quickly identified and handled appropriately (ie, in a Biosafety Level 3 facility). Serological tests including immunodiffusion and complement fixation are widely used for the detection of antibody against Coccidioides. Serology for Coccidioides can be limited by delays in antibody development or nonspecificity due to cross-reactions with other fungi. In addition, immunodiffusion and complement fixation tests are highly labor intensive and are generally limited to reference laboratories. Molecular methods can identify Coccidioides species directly from clinical specimens, allowing for a more rapid diagnosis. Fungal culture should also be performed since the isolate may be needed for antifungal susceptibility testing.

Useful For: Rapid detection of Coccidioides DNA, preferred method An aid in diagnosing coccidioidomycosis

Interpretation: A positive result indicates presence of Coccidioides DNA. A negative result indicates absence of detectable Coccidioides DNA.

Reference Values: Not applicable

Paraffin

Clinical Information: Coccidioidomycosis is caused by the dimorphic fungi, Coccidioides immitis and Coccidioides posadasii. These organisms are endemic to the southwestern regions of the United States, northern Mexico, and areas of Central and South America. The illness commonly manifests as a self-limited upper respiratory tract infection, but can also result in disseminated disease that may be refractory to treatment.(1) Clinical onset generally occurs 10 to 16 days following inhalation of coccidioidal spores (arthroconidia).(2) Disease progression may be rapid in previously healthy or immunosuppressed individuals. At present, the gold standard for the diagnosis of coccidioidomycosis is culture of the organism from clinical specimens. Culture is highly sensitive and, with the implementation of DNA probe assays for confirmatory testing of culture isolates, yields excellent specificity.(3) However, growth in culture may take up to several weeks. This often delays the diagnosis and treatment of infected individuals. Serological tests including immunodiffusion and complement fixation are widely used for the detection of antibody against Coccidioides. Serology for Coccidioides can be limited by delays in antibody development or nonspecificity due to cross-reactions with other fungi. In addition, immunodiffusion and complement fixation tests are highly labor intensive and are generally limited to reference laboratories. Molecular methods can identify Coccidioides species directly from clinical specimens and should be used in conjunction with culture. For specimen types such as formalin-fixed, paraffin-embedded tissue, culture is not possible, but the molecular test may provide useful information.

Useful For: Rapid detection of Coccidioides DNA An aid in diagnosing coccidioidomycosis

Interpretation: A positive result indicates presence of Coccidioides DNA. A negative result indicates absence of detectable Coccidioides DNA.

Reference Values: Not applicable


Cockatiel Droppings IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values: <0.35 kU/L

Cockatiel Feathers IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values: <0.35 kU/L
Cocklebur, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Cockroach, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt;or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Coconut IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Coconut, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to...
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Codfish, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.


**Q10 87853**

**Coenzyme Q10, Reduced and Total, Plasma**

**Clinical Information:** Coenzyme Q10 (CoQ10) is an essential cofactor in the mitochondrial respiratory chain responsible for oxidative phosphorylation, where it functions as an electron carrier and acts as an antioxidant. It is found in all cell membranes and is carried by lipoproteins in the circulation. Approximately 60% of CoQ10 is associated with low-density lipoprotein (LDL), 25% with high-density lipoprotein (HDL), and 15% with other lipoproteins. CoQ10 is present in the body in both the reduced and oxidized forms, with the antioxidant activity of CoQ10 dependent not only on its concentration, but also on its reduction-oxidation (redox) status. Primary CoQ10 deficiency, although rare, is characterized by neurological symptoms (seizures, developmental delay, ataxia, etc) and muscle weakness. At least 5 different phenotypes of primary CoQ10 deficiency have been described: -Encephalomyopathy (elevated serum creatine kinase [CK], recurrent myoglobinuria, lactic acidosis) -Childhood-onset cerebellar ataxia and atrophy (neuropathy, hypogonadism) -Multisystemic infant form (nystagmus, optic atrophy, sensorineural hearing loss, dystonia, rapidly progressing nephropathy) -Glomerulopathy -Myopathy (exercise intolerance, fatigue, elevated serum CK) Treatment with CoQ10 in patients with mitochondrial cytopathies can improve mitochondrial respiration in both brain and skeletal muscle. CoQ10 has been implicated in other disease processes, including Parkinson disease, diabetes, and Alzheimer disease, as well as in aging and oxidative stress. CoQ10 may also play a role in hydroxymethylglutaryl-CoA reductase inhibitor (statin) therapy; changes in CoQ10 may be relevant to statin-induced myalgia. The redox status of CoQ10 may be a useful early marker for the detection of oxidative LDL modification.

**Useful For:** Diagnosis of coenzyme Q10 (CoQ10) deficiency in mitochondrial disorders Monitoring patients receiving statin therapy Monitoring CoQ10 status during treatment of various degenerative conditions including Parkinson and Alzheimer disease

**Interpretation:** Abnormal results are reported with a detailed interpretation including an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available, and a phone number to reach a laboratory director in case the referring physician has additional questions.

**Reference Values:**
CoQ10 REDUCED
<18 years: 320-1,376 mcg/L
> or =18 years: 415-1,480 mcg/L

CoQ10 TOTAL
<18 years: 320-1,558 mcg/L
Coenzyme Q10, Total, Plasma

Clinical Information: Coenzyme Q10 (CoQ10) is an essential cofactor in the mitochondrial respiratory chain responsible for oxidative phosphorylation, where it functions as an electron carrier and also acts as an antioxidant. It is found in all cell membranes and carried by lipoproteins in the circulation. Approximately 60% of CoQ10 is associated with low-density lipoprotein (LDL), 25% with high-density lipoprotein (HDL), and 15% with other lipoproteins. CoQ10 is present in the body in both the reduced and oxidized forms, with the antioxidant activity of CoQ10 dependent not only on its concentration, but also on its reduction-oxidation (redox) status. Primary CoQ10 deficiency, although rare, is characterized by neurological symptoms (seizures, developmental delay, ataxia, etc) and muscle weakness. At least 5 different phenotypes have been described: -Encephalomyopathy (elevated serum creatine kinase [CK], recurrent myoglobinuria, lactic acidosis) -Childhood-onset cerebellar ataxia and atrophy (neuropathy, hypogonadism) -Multisystemic infant form (nystagmus, optic atrophy, sensorineural hearing loss, dystonia, rapidly progressing nephropathy) -Glomerulopathy -Myopathy (exercise intolerance, fatigue, elevated serum CK) Treatment with CoQ10 in patients with mitochondrial cytopathies improves mitochondrial respiration in both brain and skeletal muscle. CoQ10 has been implicated in other disease processes, including Parkinson disease, diabetes, and Alzheimer disease, as well as in aging and oxidative stress. CoQ10 may also play a role in hydroxymethylglutaryl-CoA reductase inhibitor (statin) therapy; changes in CoQ10 may be relevant to statin-induced myalgia. This test can be used for hemolyzed specimens to provide accurate quantitation of total coenzyme Q10.

Useful For: Diagnosis of coenzyme Q10 (CoQ10) deficiency in mitochondrial disorders Monitoring patients receiving statin therapy Monitoring CoQ10 status during treatment of various degenerative conditions including Parkinson and Alzheimer disease This test can be used for hemolyzed specimens to provide accurate quantitation of total coenzyme Q10.

Interpretation: Abnormal results are reported with a detailed interpretation including an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

Reference Values:

<table>
<thead>
<tr>
<th>Age</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18 years</td>
<td>320-1,558 mcg/L</td>
</tr>
<tr>
<td>≥18 years</td>
<td>433-1,532 mcg/L</td>
</tr>
</tbody>
</table>


**Clinical References:**

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**FCOFE**

**Coffee (Coffea spp) IgE**

**Interpretation:**

<table>
<thead>
<tr>
<th>Class IgE (kU/L)</th>
<th>Comment</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.10</td>
<td>Negative</td>
<td>0/1 0.1 â€“ 0.34 Equivocal 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.4 Moderate Positive 3 3.5 â€“ 17.4 High Positive 4 17.5 â€“ 49.9 Very High Positive 5 50.0 â€“ 99.9 Very High Positive 6 &gt;=100 Very High Positive</td>
</tr>
</tbody>
</table>

**Reference Values:**

<0.35 kU/L

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**CATR**

**Cold Agglutinin Titer, Serum**

**Clinical Information:** The cold agglutinin titer test is to be used as a tool in the evaluation of suspected cold agglutinin syndrome. In this syndrome, cold agglutinins, usually IgM with anti-I specificity, attach to the patient's erythrocytes causing a variety of symptoms. Symptoms may include chronic anemia due to premature removal of the sensitized erythrocytes from circulation by hemolysis, to acrocyanosis of the ears, fingers, or toes due to local blood stasis in the skin capillaries.

**Useful For:** Detection of cold agglutinins in patients with suspected cold agglutinin disease

**Interpretation:** Patients with cold agglutinin syndrome usually exhibit a titer value greater than 1:512, with rare cases reportedly as low as 1:64. Normal individuals often have low levels of cold agglutinins. The test is not a direct measure of clinical significance and must be used in conjunction with other in vitro and in vivo parameters.

**Reference Values:**<1:64

**Clinical References:**

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**COLIV**

**Collagen IV (COL4) Immunostain, Technical Component Only**

**Clinical Information:** Collagen IV stains the basal lamina of capillaries as well as basement membrane structures in all organs. In the kidney, the antibody stains the glomerular and tubular basement membranes and also mesangial cells and matrix within the glomerulus.

**Useful For:** A marker of the basal lamina of capillaries and basement membranes in all organs

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with
the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**FFTYC 91496**

**Collagen Type II Antibodies**

**Interpretation:** Anti-collagen II antibodies occur in 22% of patients with idiopathic SNHL, 30% of patients with sudden deafness and 20% of patients with Meniere’s disease. Anti-collagen II antibodies also occur in patients with relapsing polychondritis and in rheumatoid arthritis.

**Reference Values:**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>&lt;20 EU/mL</td>
</tr>
<tr>
<td>Borderline/Equivocal</td>
<td>20-25 EU/mL</td>
</tr>
<tr>
<td>Positive</td>
<td>&gt;25 EU/mL</td>
</tr>
</tbody>
</table>

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**CRMWS 83107**

**Collapsin Response-Mediator Protein-5-IgG (CRMP-5-IgG)**

**Western Blot, Serum**

**Clinical Information:** Autoantibodies specific for neurons and muscle are important serological markers of neurological autoimmunity. Most are highly predictive of specific neoplasms that are metastatic when diagnosed, but usually limited in spread to regional lymph nodes and adjacent structures.(1-4) Collapsin response-mediator protein-5 (CRMP-5) is highly expressed in small-cell lung carcinomas (SCLC), in neurons throughout the adult central and peripheral nervous system, and in a subset of glial cells.(1) In Western blot analyses the native antigen is a 62-kDa protein (recombinant human CRMP-5 is 68-kDa).(1) CRMP-5-IgG (also known as anti-CV-2)(4,5) is a more common autoantibody accompaniment of SCLC than antineuronal nuclear antibodies-1 (ANNA-1; anti-Hu) and sometimes occurs with thymoma. The neurological presentation of CRMP-5 seropositive patients is usually multifocal, and can affect any level of the neuraxis. Neurological presentations that suggest a CRMP-5-IgG-related syndrome include subacute chorea or cranial neuropathy (particularly loss of vision, taste, or smell), dementia, myelopathy and gastrointestinal dysmotility in a patient with risk factors for lung cancer, or encephalopathy or neuromuscular hyperexcitability in a patient with serological or clinical evidence of myasthenia gravis.(1) Fourteen percent of patients have thromboembolic phenomena. Seropositive patients who have thymoma usually present with other myasthenia gravis neurological manifestations (eg, encephalopathy, disorders of continuous muscle fiber activity).(3) CRMP-5-IgG is defined in serum or spinal fluid (CSF) by its characteristic immunofluorescence (IF) staining pattern on a mixed tissue substrate of adult mouse central and peripheral neurons. However, CRMP-5-IgG is not detectable by standard IF screening if the titer is low (serum <1:240; CSF <1:2) or if coexisting autoantibodies, either neuron-specific or nonorgan-specific antinuclear and antimitochondrial antibodies, preclude identification of CRMP-5-IgG with certainty. In these situations, CRMP-5-IgG may be detected by Western blot analysis.

**Useful For:** This testing is recommended in cases of chorea, vision loss, cranial neuropathy and myelopathy. It is recommended that PAVAL - Paraneoplastic Autoantibody Evaluation be ordered in conjunction with this test if not previously performed. Western blot analysis is indicated when interfering nonorgan-specific or coexisting neuron-specific autoantibodies in serum or spinal fluid preclude
unambiguous detection of CRMP-5-IgG, by indirect immunofluorescence assay, or when the immunofluorescence assay is negative in a patient whose neurological presentation suggests a CRMP-5-IgG-related syndrome.

**Interpretation:** A positive result confirms that a patient's subacute neurological disorder has an autoimmune basis, and is likely to be associated with a small-cell lung carcinoma (SCLC) or thymoma, which may be occult.(1,2) A positive result has a predictive value of 90% for neoplasm (77% SCLC, 6% thymoma [1]). Seropositivity is found in approximately 3% of patients who have SCLC with limited metastasis without evidence of neurological autoimmunity.(6) Clinical-serological correlations have not yet been established for children. Western blot analysis is indicated when interfering nonorgan-specific or coexisting neuron-specific autoantibodies in serum or spinal fluid preclude unambiguous detection of CRMP-5-IgG by indirect immunofluorescence assay, or when the immunofluorescence assay is negative in a patient whose neurological presentation suggests a CRMP-5-IgG-related syndrome.

**Reference Values:**
Negative (reported as positive or negative)

**Clinical References:**

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**CRMWC**

**Collapsin Response-Mediator Protein-5-IgG (CRMP-5-IgG) Western Blot, Spinal Fluid**

**Clinical Information:** Autoantibodies specific for neurons and muscle are important serological markers of neurological autoimmunity. Most are highly predictive of specific neoplasms that are metastatic when diagnosed, but usually limited in spread to regional lymph nodes and adjacent structures.(1-4) CRMP-5 is highly expressed in small-cell lung carcinomas (SCLC), in neurons throughout the adult central and peripheral nervous system, and in a subset of glial cells.(1) In Western blot analyses, the native antigen is a 62-kDa protein (recombinant human CRMP-5 is 68 kDa).(1) CRMP-5-IgG (also known as "anti-CV-2") is a more common autoantibody accompaniment of SCLC than ANNA-1 ("anti-Hu") and sometimes occurs with thymoma. The neurological presentation of CRMP-5 seropositive patients is usually multifocal, and can affect any level of the neuraxis. Neurological presentations that suggest a CRMP-5-IgG-related syndrome include subacute chorea or cranial neuropathy (particularly loss of vision, taste, or smell), dementia, myelopathy and gastrointestinal dysmotility in a patient with risk factors for lung cancer, or encephalopathy or neuromuscular hyperexcitability in a patient with serological or clinical evidence of myasthenia gravis.(1) Fourteen percent of patients have thromboembolic phenomena. Seropositive patients who have thymoma usually present with other myasthenia gravis neurological manifestations (eg, encephalopathy, disorders of continuous muscle fiber activity).(3) CRMP-5-IgG is defined in serum or spinal fluid by its characteristic immunofluorescence (IF) staining pattern on a mixed tissue substrate of adult mouse central and peripheral neurons. However, CRMP-5-IgG is not detectable by standard IF screening if the titer is low (serum <1:240; CSF <1:2) or if coexisting autoantibodies, either neuron-specific or nonorgan-specific antinuclear and antimitochondrial antibodies, preclude identification of CRMP-5-IgG with certainty. In these situations, CRMP-5-IgG may be detected by Western blot analysis.

**Useful For:** This testing is recommended in cases of chorea, vision loss, cranial neuropathy and myelopathy. It is recommended that PAVAL - Paraneoplastic Autoantibody Evaluation be ordered in conjunction with this test if not previously performed. Western blot analysis is indicated when interfering nonorgan-specific or coexisting neuron-specific autoantibodies in serum or spinal fluid preclude unambiguous detection of CRMP-5-IgG, by indirect immunofluorescence assay, or when the
immunofluorescence assay is negative in a patient whose neurological presentation suggests a CRMP-5-IgG-related syndrome.

**Interpretation:** A positive result confirms that a patient's subacute neurological disorder has an autoimmune basis and is likely to be associated with a small-cell lung carcinoma (SCLC) or thymoma, which may be occult.(1,2) A positive result has a predictive value of 90% for neoplasm (77% SCLC, 6% thymoma[1]). Seropositivity is found in approximately 3% of patients who have SCLC with limited metastasis without evidence of neurological autoimmunity.(6) Clinical-serological correlations have not yet been established for children.

**Reference Values:**

Negative (reported as positive or negative)


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**MITOT 65212**

**Combined Mitochondrial Analysis, Mitochondrial Full Genome and Nuclear Gene Panel**

**Clinical Information:** The mitochondrion occupies a unique position in eukaryotic biology. It is the site of energy metabolism, and it is the sole subcellular organelle that is composed of proteins derived from 2 genomes, mitochondrial and nuclear. A group of hereditary disorders due to mutations in either the mitochondrial genome or nuclear mitochondrial genes have been well characterized. The diagnosis of mitochondrial disease can be particularly challenging as the presentation can occur at any age, involve virtually any organ system, and be associated with widely varying severities. Due to the considerable overlap in the clinical phenotypes of various mitochondrial disorders, it is often difficult to distinguish these specific inherited disorders without genetic testing. This test utilizes massively parallel sequencing, also termed next-generation sequencing (NGS), to analyze 176 nuclear-encoded genes implicated in mitochondrial disease and to determine the exact sequence of the entire 16,569 base-pair mitochondrial genome. The utility of this test is to assist in the diagnosis of mitochondrial diseases that result from mutations in both nuclear encoded genes and in the mitochondrial genome. Those diseases involving nuclear genes include disorders of mitochondrial protein synthesis, coenzyme Q10 biosynthesis, respiratory chain complexes, and mtDNA maintenance (ie, mitochondrial DNA depletion disorders). Disorders of the mitochondrial genome include those caused by point mutations, such as mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibers (MERRF), mitochondrial myopathy (MM), neurogenic muscle weakness, ataxia, and retinitis pigmentosa (NARP), Leigh syndrome, Leber hereditary optic neuropathy (LHON), and chronic progressive external ophthalmoplegia (CPEO). In addition to the detection of single base changes with these disorders, large deletions, such as those associated with Kearns-Sayre or Pearson syndromes, are also detected. In contrast to mutations in nuclear genes, which are present in either 0, 1, or 2 copies, mitochondrial mutations can be present in any fraction of the total organelles, a phenomenon known as heteroplasmy. Typically, the severity of disease presentation is a function of the degree of heteroplasmy. Individuals with a higher fraction of mutant mitochondria present with more severe disease than those with lower percentages of mutant alleles. The sensitivity for the detection of mutant alleles in a background of wild-type (or normal) mitochondrial sequences by NGS is approximately 10%. See Targeted Genes Interrogated by Mitochondrial Nuclear Gene Panel in Special Instructions for details regarding the targeted nuclear genes identified by this test.

**Useful For:** Diagnosis of mitochondrial disease that results from mutations in either nuclear-encoded genes or the mitochondrial genome A second-tier test for patients in whom previous targeted gene mutation analyses for specific mitochondrial disease-related genes were negative Identification of mutations known to be associated with mitochondrial disease, allowing for predictive testing of at-risk
**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. For mitochondrial DNA (mtDNA) alterations, the degree of heteroplasmy of each single nucleotide or INDEL variant, defined as the ratio (percentage) of variant sequence reads to the total number of reads, will also be reported. Large mtDNA deletions will be reported as either homoplasmic or heteroplasmic, but the degree of heteroplasmy will not be estimated, due to possible preferential amplification of the smaller deletion product by long-range PCR.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Common Millet, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
</tbody>
</table>

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Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com

Common Reed, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

Common Variable Immunodeficiency Confirmation Flow Panel

Clinical Information: Common variable immunodeficiency (CVID) is the most prevalent primary immunodeficiency with a prevalence of CVID of 1:25,000 to 1:50,000.(1) It has a bimodal presentation with a subset presenting in early childhood and a second set presenting between 15 and 40 years of age or even later. CVID is characterized by hypogammaglobulinemia usually involving most or all of the immunoglobulin (Ig) classes (IgG, IgA, IgM, and IgE), impaired functional antibody responses, and recurrent sinopulmonary infections.(1) B cell numbers are usually normal, although a minority of patients (5%-10%) have very low B cell counts (<1% of peripheral blood leukocytes). It is reasonable to suspect a transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) defect in patients with low to absent IgA, low IgG, and low or normal IgM, along with splenomegaly, autoimmune cytopenias, autoimmune thyroiditis, and tonsillar hypertrophy. In TACI-deficient patients, there may be an increased risk for developing neoplasias such as non-Hodgkin lymphoma or other solid tumors. CD19 defects result in absence of B cells expressing CD19. When an alternative B-cell marker such as CD20 is used, however, B cells can be detected in the blood of these patients. Inducible T-cell costimulator (ICOS)-deficiency results in reduced class-switched memory B-cells. Of all patients with CVID, 25% to 30% have increased numbers of CD8 T cells and a reduced CD4/CD8 ratio (<1).(1) A subset (5%-10%) exhibit noncaseating, sarcoid-like granulomas in different organs and also tend to develop a progressive T cell deficiency.(1) Patients with mutations in the TACI gene (see below) are particularly prone to developing autoimmune disease, including cytopenias as well as lymphoproliferative disease. The etiology of CVID is heterogeneous, but recently 4 genetic defects were described that are associated with the CVID phenotype. Specific mutations, all of which are expressed on B cells, have been implicated in the pathogenesis of CVID. These mutations encode for: -ICOS: inducible costimulator expressed on activated T cells(2) -TACI: transmembrane activator and calcium modulator and cyclophilin ligand (CAML) interactor(3) -CD19(4) -BAFF-R: B-cell activating factor belonging to the tumor necrosis factor (TNF) receptor family(5) Of these, mutations of the gene that encodes TACI, TNFRSF13B (tumor necrosis factor receptor superfamily, member 13B), probably account for about 10% to 15% of all CVID cases.(3) Patients with mutations in the TACI gene are particularly prone to developing autoimmune disease, including cytopenias, as well as lymphoproliferative disease. The other mutations each have been reported in only a handful of patients. The etiopathogenesis is still undefined in more than 75% to 80% of CVID patients. A BAFF-R defect should be suspected in patients with low to very low class switched and nonswitched memory B cells and very high numbers of transitional B cells (see IABC / B-Cell Phenotyping Screen for Immunodeficiency and Immune Competence Assessment, Blood). Class switching is the process that allows B cells, which possess IgD and IgM on their cell surface as a part of the antigen-binding complex, to produce IgA, IgE, or IgG antibodies. A TACI defect is suspected in patients with low IgA and low IgG with normal to low switched B cells, with autoimmune or lymphoproliferative manifestations or both, and normal B cell responses to mitogens.

Useful For: Screening for common variable immunodeficiency (CVID) Identifying defects in TACI and BAFF-R in patients presenting with clinical symptoms and other laboratory features consistent with CVID Evaluating B cell immune competence by assessing expression of BAFF-R and TACI proteins Useful for assessing BAFF-R and TACI protein expression and frequency of B cells bearing these receptors. TNFRSF13C (BAFF-R) and TNFRSF13B (TACI) gene mutations have been described in a small subset of patients with humoral immunodeficiencies classified as CVID. The majority of TNFRSF13B mutations preserve TACI protein expression and require genetic testing to identify pathogenic or potentially pathogenic mutations/variants.

Interpretation: BAFF-R is normally expressed on over 95% of B cells, while TACI is expressed on a smaller subset of B cells (3%-70%) and some activated T cells. Expression on B cells increases with B cell activation. The lack of TACI or BAFF-R surface expression on B cells is suggestive of a potential common variable immunodeficiency (CVID)-associated defect, if other features of CVID are present. The majority of TACI mutations (>95%) preserve protein expression but abrogate protein function, hence the only way to conclusively establish a TACI mutational defect is to perform genetic testing (TACIF / Transmembrane Activator and CAML Interactor [TACI] Gene, Full Gene Analysis).

Reference Values:

%CD19+TACI+: >3.4%

Complement 4d (C4d, Comp 4d) Immunostain, Technical Component Only

Clinical Information: Complement 4d (C4d) is a split product resulting from complement activation. The deposition of C4d on the walls of peritubular capillaries in kidney allografts or capillaries in cardiac allografts has been associated with antibody-mediated transplant rejection.

Useful For: Aids in the identification of antibody-mediated transplant rejection

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Complement C1q, Serum

Clinical Information: The first component of complement (C1) is composed of 3 subunits designated as C1q, C1r, and C1s. C1q recognizes and binds to immunoglobulin complexed to antigen and initiates the complement cascade. Congenital deficiencies of any of the early complement components (C1, C2, C4) results in an inability to clear immune complexes. Inherited deficiency of C1 is rare. Like the more common C2 deficiency, C1 deficiency is associated with increased incidence of immune complex disease (systemic lupus erythematosus, polymyositis, glomerulonephritis, and Henoch-Schonlein purpura). Low C1 levels have also been reported in patients with abnormal immunoglobulin levels (Bruton's and common variable hypogammaglobulinemia and severe combined immunodeficiency), and this is most likely due to increased catabolism. The measurement of C1q is an indicator of the amount of C1 present.

Useful For: Assessment of an undetectable total complement (CH50) level Diagnosing congenital C1 (first component of complement) deficiency Diagnosing acquired deficiency of C1 inhibitor
Interpretation: An undetectable C1q in the presence of an absent total complement (CH50) and normal C2, C3, and C4 suggests a congenital C1 (first component of complement) deficiency. A low C1q in combination with a low C1 inhibitor and low C4 suggests an acquired C1 inhibitor deficiency.

Reference Values:
12-22 mg/dL


C3

Complement C3, Serum

Clinical Information: The complement system is an integral part of the body's immune defenses. The primary complement pathway consists of recognition (Clq, Clr, Cls), activation (C4, C2, C3), and attack (C5, C6, C7, C8, C9) mechanisms with respect to their role in antibody-mediated cytolysis. The complement system can be activated via immune complexes, and the alternative pathway (properdin pathway), which is activated primarily by foreign bodies such as microorganisms. C3 activation involves cleavage by C3 convertase into C3a and C3b. When immune complexes are not involved, the alternate method of complement activation initiates the reactant sequence at C3, bypassing C1, C4, and C2. Severe recurrent bacterial infections occur in patients with homozygous C3 deficiency and in those patients with low levels of C3 secondary to the absence of C3b activator. Decreased C3 may be associated with acute glomerulonephritis, membranoproliferative glomerulonephritis, immune complex disease, active systemic lupus erythematosus, septic shock, and end-stage liver disease.

Useful For: Assessing disease activity in systemic lupus erythematosus (SLE) Investigating an undetectable total complement (CH50) level

Interpretation: A decrease in C3 levels to the abnormal range is consistent with disease activation in systemic lupus erythematosus (SLE).

Reference Values:
75-175 mg/dL


C4

Complement C4, Serum

Clinical Information: The complement system is an integral part of the immune defenses. It can be activated via immune complexes (classic pathway) or by bacterial polysaccharides (alternative pathway). The classic complement pathway consists of recognition, (C1q, C1r, C1s), activation (C2, C3, C4), and attack (C5, C6, C7, C8, C9) mechanisms with respect to their role in antibody-mediated cytolysis. C4 is one of the activation proteins of the classic pathway. In the absence of C4, immune complexes will not be cleared by C3 activation peptides, but bacterial infections can still be defended via the alternative pathway. C4 may be decreased in systemic lupus erythematosus, early glomerulonephritis, immune complex disease, cryoglobulinemia, hereditary angioedema, and congenital C4 deficiency.

Useful For: Investigating an undetectable total complement (CH50) Confirming hereditary angioedema (with low C1 inhibitor) Assessing disease activity in systemic lupus erythematosus, proliferative glomerulonephritis, rheumatoid arthritis, and autoimmune hemolytic anemia

Interpretation: C4 levels will be decreased in acquired autoimmune disorders, in active phase of lupus erythematosus, and in rheumatoid arthritis An undetectable C4 level (with normal C3) suggests a...
congenital C4 deficiency Levels will be increased in patients with autoimmune hemolytic anemia

**Reference Values:**
14-40 mg/dL

**Clinical References:**

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**Complement, Alternate Pathway (AH50), Functional, Serum**

**Clinical Information:** Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: (1) the classic pathway, (2) the alternative (or properdin) pathway, and (3) the lectin activation (or mannose-binding protein: MBP) pathway. The total hemolytic complement (CH50) assay (COM / Complement, Total, Serum) is the best screening assay for most complement abnormalities. It assesses the classical complement pathway including early components that activate the pathway in response to immune complexes, as well as the late components involved in the membrane attack complex. The CH50 assay will be abnormal if there are specific hereditary or acquired C1-C9 complement component deficiencies or if there is consumption of complement due to immune (or autoimmune) complexes. The complement alternate pathway (AH50) assay is a screening test for complement abnormalities in the alternative pathway. The alternate pathway shares C3 and C5-C9 components, but has unique early complement components designated factors D, B, and P, as well as regulatory factors H and I. This pathway is activated by microbial polysaccharides and does not require immune complex formation. Patients with disseminated infections with pyogenic bacteria in the presence of a normal CH50 may have an absent AH50 due to hereditary or acquired deficiencies of the alternate pathway. Patients with deficiencies in the alternate pathway factors (D, B, P, H, and I) or late complement components (C3, C5-C9) are unusually susceptible to recurrent neisserial meningitis. The use of the CH50 and AH50 assays allow identification of the specific pathway abnormality. Unregulated alternative pathway can also result in disease. The majority of these diseases present with renal function impairment such as atypical hemolytic uremic syndrome (a-HUS), dense deposit disease (DDD), and C3 glomerulonephritis (C3GN).

**Useful For:** Investigation of suspected alternative pathway complement deficiency, atypical hemolytic uremic syndrome, C3 glomerulonephritis, dense-deposit disease

**Interpretation:** Absent complement alternate pathway (AH50) in the presence of a normal total hemolytic complement (CH50) suggests an alternate pathway component deficiency. Normal AH50 with absent CH50 suggests an early (C1, C2, C4) classic pathway deficiency. Absent AH50 and CH50 suggests a late (C3, C5, C6, C7, C8, C9) component deficiency or complement consumption. Absent AH50 and CH50 in the presence of a normal C3 and C4 suggests a late (C5, C6, C7, C8, C9) component deficiency.

**Reference Values:**
> or =46% normal

**Clinical References:**

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**Complement, Total, Serum**

**Clinical Information:** Complement proteins are components of the innate immune system. There are 3 pathways to complement activation: (1) the classic pathway, (2) the alternative (or properdin) pathway, and (3) the lectin activation (or mannose-binding protein) pathway. The classic pathway of the complement
system is composed of a series of proteins that are activated in response to the presence of immune complexes. The activation process results in the generation of peptides that are chemotactic for neutrophils and that bind to immune complexes and complement receptors. The end result of the complement activation cascade is the formation of the lytic membrane attack complex (MAC). The absence of early components (C1, C2, C3, C4) of the complement cascade results in the inability of immune complexes to activate the cascade. Patients with deficiencies of the early complement proteins are unable to generate the peptides that are necessary to clear immune complexes and to attract neutrophils or to generate lytic activity. These patients have increased susceptibility to infections with encapsulated microorganisms. They may also have symptoms that suggest autoimmune disease, and complement deficiency may be an etiologic factor in the development of autoimmune disease. Patients with deficiencies of the late complement proteins (C5, C6, C7, C8, and C9) are unable to form the MAC, and may have increased susceptibility to neisserial infections. Undetectable complement levels are found in patients with specific component deficiencies. Decreased complement levels are found in infectious and autoimmune diseases due to fixation and consumption of complement.

Useful For: Detection of individuals with an ongoing immune process First-order screening test for congenital complement deficiencies

Interpretation: Low levels of total complement (total hemolytic complement CH50) may occur during infections, disease exacerbation in patients with systemic lupus erythematosus, and in patients with immune complex diseases such as glomerulonephritis. Undetectable levels suggest the possibility of a complement component deficiency. Individual complement component assays are useful to identify the specific deficiency.

Reference Values:
> or =16 years: 30-75 U/mL

Reference values have not been established for patients that are <16 years of age.


AHUSP 64663

Complement-Mediated Atypical Hemolytic-Uremic Syndrome (aHUS)/Thrombotic Microangiopathy (TMA) Gene Panel

Clinical Information: Complement-mediated hemolytic uremic syndrome, also known as atypical hemolytic uremic syndrome (aHUS), is a well-recognized disease entity characterized by complement activation in the microvasculature. Abnormalities of the alternate pathway of complement, which may be inherited (genetic) or acquired, underlie both the sporadic and familial forms of the disease and are identified in at least two-thirds (approximately 60%) of patients. Unlike many other monogenic disorders of the immune system, multiple hits may be required for disease manifestation, which may include a trigger event (transplantation, pregnancy, malignant hypertension, autoimmune disorders, sepsis, malignancy, etc), and 1 or more contributing genetic variants or haplotypes in the alternate pathway complement genes. The overall prognosis is poor with most patients developing end-stage renal disease (ESRD) or permanent kidney injury within 1 year of diagnosis despite plasma exchange (PLEX/PEX) or plasma infusion (PI) therapy. Renal transplantation in most patients is also associated with a poor prognosis with loss of the allograft. Drugs targeting the complement pathway, notably Eculizumab, have achieved success in modulating clinical remission and there are a few reports of combined liver-kidney transplants for these patients. Newer therapies are also likely to emerge over time. Individuals with genetic aHUS frequently experience relapse even after complete recovery following the presenting episode. Complement-mediated HUS presents with clinical features that are nearly identical to thrombotic thrombocytopenic purpura (TTP) and Shiga-toxin HUS (ST-HUS), making laboratory differentiation essential. TTP is a rare clinical entity but is an important diagnosis as it is associated with very high mortality (90%) if untreated. Mortality can be reduced by early PLEX. Congenital TTP is due to genetic defects in the ADAMTS13 gene, while acquired TTP is related to
autoantibodies against ADAMTS13, which reduces function. While TTP was initially characterized by thrombocytopenia, microangiopathic hemolytic anemia (MAHA), fluctuating neurological signs, renal failure and fever, the disease can present with only some of these features. The thrombotic microangiopathies (TMA) cover both aHUS and TTP and the clinical distinctions are not always clear-cut. Besides the thrombocytopenia, which is one of the key features of TMA, there is presence of schistocytes and highly increased levels of lactate dehydrogenase (LDH). Complement-mediated HUS is considered genetic when 2 or more members of the same family are affected by the disease at least 6 months apart and exposure to a common triggering infectious agent has been excluded, or when pathogenic variants are identified in 1 or more of the genes known to be associated with aHUS, irrespective of familial history. A patient may have both autoantibodies to complement alternate pathway proteins and genetic defects in these genes. It is important to note that certain genetic defects in these genes, eg, complement C3 (C3), may be associated with a more classic immunodeficiency phenotype with recurrent infections with encapsulated pathogens and connective tissue diseases with no evidence of aHUS/TMA. Table 1. Genes included in the Complement aHUS/TMA PID Gene Panel

**GENE SYMBOL (ALIAS) PROTEIN OMIM INCIDENCE INHERITANCE PHENOTYPE**

| Disorder | ADAMTS13 A disintegrin and metalloproteinase with thrombospondin motifs 13 isoform 1 preproprotein 604134 | Not available | AR Familial thrombotic thrombocytopenic purpura C3 | C3 deficiency (AR), susceptibility to aHUS (AD) CD46 (MCP) Membrane cofactor protein isoform 1 precursor 120920 | Approximately 5% of aHUS AD, AR C3 deficiency (AR), susceptibility to aHUS (AD) | Complement factor B (CFB) Complement factor B precursor 138470 | Rare AD Susceptibility to aHUS | Complement factor C3 (C3) | Approximately 5% of aHUS AD, AR C3 deficiency (AR), susceptibility to aHUS (AD) | Membrane cofactor protein (MCP) isoform 1 precursor 120920 | Approximately 12% of aHUS AD, AR Susceptibility to aHUS 2 CFB Complement factor B | Membrane cofactor protein (MCP) isoform 1 precursor 120920 | Approximately 5% of aHUS AD, AR C3 deficiency (AR), susceptibility to aHUS (AD) | Complement factor H (CFH) Complement factor H isoform a precursor 134370 | Approximately 30% of aHUS patients AD, AR Complement factor H deficiency, susceptibility to aHUS 1 CFHR1 Complement factor H-related protein 1 precursor 134371 | Rare AD, AR Susceptibility to aHUS CFHR3 Complement factor H-related protein 3 isoform 1 precursor 605336 | Rare AD, AR Susceptibility to aHUS CFHR3 Complement factor H-related protein 3 isoform 1 precursor 605336 | Rare AD, AR Susceptibility to aHUS CFHR5 Complement factor H-related protein 5 precursor 608593 | Rare AD, AR Susceptibility to aHUS CFHR5 Complement factor H-related protein 5 precursor 608593 | Rare AD, AR Susceptibility to aHUS CFHR5 Complement factor H-related protein 5 precursor 608593 | Rare AD, AR Susceptibility to aHUS CFHR5 Complement factor H-related protein 5 precursor 608593 | Rare AD, AR Susceptibility to aHUS CFHR5 Complement factor H-related protein 5 precursor 608593 | Rare AD, AR Susceptibility to aHUS CFHR5 Complement factor H-related protein 5 precursor 608593 | Rare AD, AR Susceptibility to aHUS CFHR5 Complement factor H-related protein 5 precursor 608593 | Rare AD, AR Susceptibility to aHUS CFHR5 Complement factor H-related protein 5 precursor 608593 |

**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of complement-mediated HUS/atypical HUS (aHUS) or thrombotic microangiopathies (TMA) Establishing a diagnosis and, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying variants in genes encoding alternate pathway components and specific coagulation pathway genes known to be associated with increased risk for aHUS/TMA allowing for predictive testing of at-risk family members

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Comprehensive Cardiomyopathy Multi-Gene Panel, Blood**

**Clinical Information:** The cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathy can be caused by inherited, genetic factors, or by nongenetic (acquired) causes such as infection or trauma. When the presence or severity of the cardiomyopathy observed in a patient cannot be explained by acquired causes, genetic testing for the inherited forms of cardiomyopathy may be considered. Overall, the cardiomyopathies are some of the most common genetic disorders. The inherited forms of cardiomyopathy include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC or AC), and left ventricular noncompaction (LVNC). The hereditary form of HCM is characterized by left ventricular hypertrophy in the absence of other causes, such as structural abnormalities, systemic hypertension, or physiologic hypertrophy due to rigorous athletic training (athlete’s heart). The incidence of HCM in the general population is approximately 1 in 500, and the hereditary form is most often caused by variants in genes encoding the components of the cardiac sarcomere. The clinical presentation of HCM can be variable, even within the same family. HCM can be asymptomatic in some individuals, but can also cause life-threatening arrhythmias that increase the risk of sudden cardiac death. DCM is established by the presence of left ventricular enlargement and systolic dysfunction. DCM may present with heart failure with symptoms of congestion, arrhythmias or conduction system disease, or thromboembolic disease (stroke). The incidence of DCM is likely higher than originally reported due to subclinical phenotypes and underdiagnosis, with recent estimates suggesting that DCM affects approximately 1 in every 250 people. After exclusion of nongenetic causes such as ischemic injury, DCM is traditionally referred to as “idiopathic” dilated cardiomyopathy. Approximately 20% to 50% of individuals with idiopathic DCM may have an identifiable genetic cause for their disease. Families with 2 or more affected individuals are diagnosed with familial dilated cardiomyopathy. Arrhythmogenic right ventricular dysplasia (ARVD or AC) is characterized by breakdown of the myocardium and replacement of the muscle tissue with fibrofatty tissue, resulting in an increased risk of arrhythmia and sudden death. Age of onset and severity are variable, but symptoms typically develop in adulthood. The incidence of ARVC is approximately 1 in 1,000 to 1 in 2,500. LVNC is characterized by left ventricular hypertrophy and prominent trabeculations of the ventricular wall, giving a spongy appearance to the muscle wall. It is thought to be caused by the arrest of normal myocardial morphogenesis. Clinical presentation is highly variable, ranging from no symptoms to congestive heart failure and life-threatening arrhythmias. An increased risk of thromboembolic events is also present with LVNC. Approximately 67% of LVNC is considered familial. Restrictive cardiomyopathy (RCM) is the rarest form of cardiomyopathy and is associated with abnormally rigid ventricular walls. Systolic function can be normal or near normal, but diastolic dysfunction is present. There are several nongenetic causes of RCM, but this condition can be familial as well, with the TNNI3 gene accounting for the majority of inherited cases. The age at presentation for familial RCM ranges from childhood to adulthood, and there is an increased risk of sudden death associated with this condition. Noonan syndrome (NS) is an autosomal dominant disorder of variable expressivity characterized by short stature, congenital heart defects, and characteristic facial dysmorphology. HCM is present in approximately 20% to 30% of individuals affected with NS. There are a number of disorders with significant phenotypic overlap with NS, including Costello syndrome, cardiofaciocutaneous (CFC) syndrome, and multiple lentigines syndrome (formerly called LEOPARD syndrome). NS and related disorders (also called the RASopathies) are caused by variants in genes involved in the RAS-MAPK signaling pathway. In some cases, variants in these genes may cause cardiomyopathy in the absence of other syndromic features. Cardiomyopathy may also be caused by an underlying systemic disease such as a mitochondrial disorder, a muscular dystrophy, or a metabolic storage disorder. In these cases, cardiomyopathy may be the first feature to come to attention clinically. The hereditary forms of cardiomyopathy are most frequently associated with an autosomal dominant form of inheritance; however, X-linked and autosomal recessive forms of disease are also present. In some cases, compound...
heterozygous or homozygous variants may be present in genes typically associated with autosomal dominant inheritance, often leading to a more severe phenotype. Digenic variants (2 different heterozygous variants at separate genetic loci) in autosomal dominant genes have also been reported to occur in patients with severe disease (particularly HCM and ARVC). The inherited cardiomyopathies display both allelic and locus heterogeneity, whereby a single gene may cause different forms of cardiomyopathy (allelic heterogeneity) and variants in different genes can cause the same form of cardiomyopathy (locus heterogeneity). This comprehensive cardiomyopathy panel includes sequence analysis of 55 genes and may be considered for individuals with HCM, DCM, ARVC, or LVNC, whom have had uninformative test results from a more targeted, disease-specific test. This test may also be helpful when the clinical diagnosis is not clear, or when there is more than 1 form of cardiomyopathy in the family history. It is important to note that the number of variants of uncertain significance detected by this panel may be higher than for the disease-specific panels, making clinical correlation more difficult. Genes included in the Comprehensive Cardiomyopathy Multi-Gene Panel Gene Protein Inheritance Disease Association ABCC9 ATP-binding cassette, subfamily C, member 9 AD DCM, Cantu syndrome ACTC1 Actin, alpha, cardiac muscle AD CHD, DCM, LVNC ACTN2 Actinin, alpha-2 AD DCM, HCM ANKRD1 Ankyrin repeat domain-containing protein 1 AD HCM, DCM BRAF V-RAF murine sarcoma viral oncogene homolog B1 AD Noonan/CFC/Costello syndrome CAV3 Caveolin 3 AD, AR HCM, LQTS, LGMD, Tateyama-type distal myopathy, rippling muscle disease CBL CAS-BR-M murine ecotropic retroviral transforming sequence homolog AD Noonan syndrome-like disorder CRYAB Crystallin, alpha-B AD, AR DCM, myofibrillar myopathy CSRP3 Cysteine-and glycine-rich protein 3 AD HCM, DCM DES Desmin AD, AR DCM, ARVC, myofibrillar myopathy, RCM with AV block, neurogenic scapuloperoneal syndrome Kaeser type, LGMD DSC2 Desmocollin AD, AR ARVC, ARVC + skin and hair findings DSG2 Desmoglein AD ARVC DSP Desmoplakin AD, AR DCM, Carvajal syndrome DTNA Dystrobrevin, alpha AD LVNC, CHD GLA Galactosidase, alpha X-linked Fabry disease HRAS V-HA-RAS Harvey rat sarcoma viral oncogene homolog AD Costello syndrome JUP Junction plakoglobin AD, AR DCM, Noonan syndrome KRAS V-KI-RAS2 Kirsten rat sarcoma viral oncogene homolog AD Noonan/CFC/Costello syndrome LAMA4 Laminin, alpha-4 AD DCM LAMP2 Lysosome-associated membrane protein 2 AD Noonan syndrome-like disorder LDB3 LIM domain-containing 3 AD DCM, LVNC, myofibrillar myopathy LMNA Lamin A/C AD, AR DCM, EMD, LGMD, congenital muscular dystrophy (see OMIM for full listing) MAP2K1 Mitogen-activated protein kinase kinase 1 AD Noonan/CFC MAP2K2 Mitogen-activated protein kinase kinase 2 AD Noonan/CFC MYBPC3 Myosin-binding protein C, cardiac muscle AD HCM, DCM MYH6 Myosin, heavy chain 6, cardiac muscle, alpha AD HCM, DCM MYH7 Myosin, heavy chain 7, cardiac muscle, beta AD HCM, DCM, LVNC, myopathy MYL2 Myosin, light cahin 2, regulatory, cardiac, slow AD HCM MYLK2 Myosin light chain 2 AD HCM MYOZ2 Myozin 2 AD HCM MYZP1 Myopalladin AD HCM, DCM NEXN Nexilin AD HCM, DCM NRAM Neuroblastoma RAS viral oncogene homolog AD Noonan syndrome PKP2 Plakophilin 2 AD ARVC PLN Phospholamban AD HCM, DCM PRKAG2 Protein kinase, AMP-activated, noncatalytic, gamma2 AD HCM, Wolff-Parkinson-White syndrome PTPN11 Proetin-tyrosine phosphatase, nonreceptor-type, 11 AD Noonan/CFC/multiple lentigines syndrome RYR2 Ryanodine receptor 2 AD ARVC, CPVT, LQTS SCN5A Sodium channel, voltage gated, type V, alpha subunit AD Brugada syndrome, DCM, Heart block, LQTS, SSS, SIDS SGCDSarcoglycan, delta AD, AR DCM, LGMD SHOC2 Suppressor of clear, C. elegans, homolog of AD Noonan syndrome-like with loose anagen hair SOSS1 Son of sevenless, dropsophil, homolog 1 AD Noonan syndrome TAZ Tafazzin X-linked Barth syndrome, LVNC, DCM TNC Tcap Titin-cap (telethonin) AD, AR HCM, DCM, LGMD TMEM43 Transmembrane protein 43 AD ARVC, EMD TNN1 Troponin I, cardiac AD, AR DCM, HCM, DCM TNN2 Troponin T2, cardiac AD HCM, DCM, TNNI3 Troponin I, cardiac AD, AR DCM, HCM, RCM TNP1 Tropomyosin 1 AD HCM, DCM, LVNC TTN Titin AD, AR HCM, DCM, ARVC, myopathy TRB Transhyretin AD Thrombocytopenia-related amyloidosis VCL Vinculin AD HCM, DCM Abbreviations: Hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), left ventricular noncompaction cardiomyopathy (LVNC), restrictive cardiomyopathy (RCM), limb-girdle muscular dystrophy (LGMD), Emery muscular dystrophy (EMD), congenital heart defect (CHD), sudden infant death syndrome (SIDS), long QT syndrome (LQTS), sick sinus syndrome (SSS), autosomal dominant (AD), autosomal recessive (AR)

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history of cardiomyopathy.
history suggestive of hereditary cardiomyopathy Establishing a diagnosis of a hereditary cardiomyopathy and, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying a pathogenic variant within a gene known to be associated with disease that allows for predictive testing of at-risk family members

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**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**CMAMA Comprehensive Metabolic Panel, Serum**

**Clinical Information:** The comprehensive metabolic panel measures 14 analytes and calculates an anion gap. It is used to assess kidney or liver status, electrolyte and acid/base balance, and blood glucose. This comprehensive metabolic panel can also provide information about a patient's response to medications that would impact kidney or liver function.

**Useful For:** Routine health monitoring Patient monitoring while hospitalized for information regarding metabolism, including the current kidney status, electrolyte and acid/base balance, and blood glucose

**Interpretation:** Comprehensive metabolic panel results are usually evaluated in conjunction with each other for patterns of results. The pattern of abnormal results can help identify the possible conditions or diseases present. Many conditions will cause abnormal results including kidney failure, breathing problems, and diabetes-related complications.

**Reference Values:**

<table>
<thead>
<tr>
<th>SODIUM</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year: not established</td>
</tr>
<tr>
<td>&gt; or =1 year: 135-145 mmol/L</td>
</tr>
</tbody>
</table>
POTASSIUM
<1 year: not established
> or =1 year: 3.6-5.2 mmol/L

CHLORIDE
<1 year: not established
1-17 years: 102-112 mmol/L
> or =18 years: 98-107 mmol/L

BICARBONATE
Males:
<1 year: not established
1-2 years: 17-25 mmol/L
3 years: 18-26 mmol/L
4-5 years: 19-27 mmol/L
6-7 years: 20-28 mmol/L
8-17 years: 21-29 mmol/L
> or =18 years: 22-29 mmol/L

Females:
<1 year: not established
1-3 years: 18-25 mmol/L
4-5 years: 19-26 mmol/L
6-7 years: 20-27 mmol/L
8-9 years: 21-28 mmol/L
> or =10 years: 22-29 mmol/L

ANION GAP
<7 years: not established
> or =7 years: 7-15

BLOOD UREA NITROGEN (BUN)
Males:
<12 months: not established
1-17 years: 7-20 mg/dL
> or =18 years: 8-24 mg/dL

Females:
<12 months: not established
1-17 years: 7-20 mg/dL
> or =18 years: 6-21 mg/dL

CREATININE
Males:
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-14 years: 0.35-0.86 mg/dL
> or =15 years: 0.74-1.35 mg/dL

Females:
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-15 years: 0.35-0.86 mg/dL
> or =16 years: 0.59-1.04 mg/dL
ESTIMATED GLOMERULAR FILTRATION RATE (eGFR)
>60 mL/min/BSA
Estimated GFR calculated using the 2009 CKD_EPI creatinine equation

CALCIUM
<1 year: 8.7-11.0 mg/dL
1-17 years: 9.3-10.6 mg/dL
18-59 years: 8.6-10.0 mg/dL
60-90 years: 8.8-10.2 mg/dL
>90 years: 8.2-9.6 mg/dL

GLUCOSE
0-11 months: not established
> or =1 year: 70-140 mg/dL

TOTAL PROTEIN
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients who are <12 months of age.

ALBUMIN
> or =12 months: 3.5-5.0 g/dL
Reference values have not been established for patients who are <12 months of age.

ASPARTATE AMINOTRANSFERASE (AST)
Males:
0-11 months: not established
1-13 years: 8-60 U/L
> or =14 years: 8-48 U/L

Females:
0-11 months: not established
1-13 years: 8-50 U/L
> or =14 years: 8-43 U/L

ALKALINE PHOSPHATASE (ALP)
Males:
4 years: 149-369 U/L
5 years: 179-416 U/L
6 years: 179-417 U/L
7 years: 172-405 U/L
8 years: 169-401 U/L
9 years: 175-411 U/L
10 years: 191-435 U/L
11 years: 185-507 U/L
12 years: 185-562 U/L
13 years: 182-587 U/L
14 years: 166-571 U/L
15 years: 138-511 U/L
16 years: 102-417 U/L
17 years: 69-311 U/L
18 years: 52-222 U/L
> or =19 years: 45-115 U/L

Females:
4 years: 169-372 U/L
5 years: 162-355 U/L
6 years: 169-370 U/L
7 years: 183-402 U/L
ALANINE AMINOTRANSFERASE (ALT)
Males:
> or =1 year: 7-55 U/L
Reference values have not been established for patients who are <12 months of age.

Females:
> or =1 year: 7-45 U/L
Reference values have not been established for patients who are <12 months of age.

TOTAL BILIRUBIN
0-6 days: Refer to http://bilitool.org/ for information on age-specific (postnatal hour of life) serum bilirubin values.
7-14 days: <15.0 mg/dL
15 days to 17 years: < or =0.9 mg/dL
>18 years: < or =1.2 mg/dL


CAH2T 42202  Congenital Adrenal Hyperplasia (CAH) Newborn Screen, Blood Spot

Clinical Information: Congenital adrenal hyperplasia (CAH) is a group of disorders caused by inherited defects in steroid biosynthesis, most commonly, 21-hydroxylase deficiency (approximately 90% of cases) and 11-beta hydroxylase deficiency (approximately 5% of cases). The overall incidence of CAH due to 21-hydroxylase deficiency is approximately 1 in 15,000 live births. Individuals with CAH may present with life-threatening salt-wasting crises in the newborn period and incorrect gender assignment of virilized females, which occurs due to in utero exposure to reduced glucocorticoids and mineralocorticoids and elevated 17-hydroxyprogesterone (17-OHP) and androgens. Hormone replacement therapy, when initiated early, results in a significant reduction in morbidity and mortality. Therefore, newborn screening for CAH is desirable and has been implemented in all 50 states. Immunoassays are typically used to quantify 17-OHP as a marker for CAH in the newborn screen setting. However, these immunoassays are hampered by cross-reactivity of the antibodies with other steroids, yielding a high rate of false-positive results. Tandem mass spectrometry (MS/MS) allows for the simultaneous specific determination of 17-OHP and other steroids, such as androstenedione, cortisol, 11-deoxycorticisol, and 21-deoxycortisol. Application of this technology to the determination of steroids in newborn blood spots significantly enhances the correct identification of patients with CAH and reduces the number of false-positive screening results when implemented as a second-tier analysis performed prior to reporting.
Useful For: Second-tier testing of newborns with abnormal screening result for congenital adrenal hyperplasia

Interpretation: Findings of a 17-hydroxyprogesterone (17-OHP) value greater than 15.0 ng/mL and a high (17-OHP + androstenedione)/cortisol ratio (> or =1) are supportive of the initial abnormal newborn screening result. Findings of an 11-deoxycortisol value greater than 15.0 ng/mL or 21-deoxycortisol greater than 4.0 ng/mL with elevated 17-OHP further support the abnormal newborn screening result and increase the diagnostic specificity. Clinical and laboratory follow-up is strongly recommended.

Reference Values:
17-HYDROXYPROGESTERONE
<15.1 ng/mL

ANDROSTENEDIONE
<3.1 ng/mL

CORTISOL
Not applicable

11-DEOXYCORTISOL
<15.1 ng/mL

21-DEOXYCORTISOL
<4.1 ng/mL

(17 OHP + ANDROSTENEDIONE)/CORTISOL RATIO
<1.1
Note: Abnormal (17 OHP + Androstenedione)/Cortisol Ratio: > or =1.1 is only applicable when 17-OHP is elevated

11-DEOXYCORTISOL/CORTISOL RATIO
Not applicable

Levels decrease rapidly to after one week.

1 - 11m

Androstenedione gradually decreases during the first six months to prepubertal levels.

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepubertal Children</td>
<td>17</td>
</tr>
<tr>
<td>Adult Males</td>
<td>44 - 186</td>
</tr>
<tr>
<td>Adult Females</td>
<td>28 - 230</td>
</tr>
<tr>
<td>Females Postmenopausal</td>
<td></td>
</tr>
</tbody>
</table>

Cortisol

Units: ug/dL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>1.0 - 11</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>2.5 - 9.1</td>
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<tr>
<td>Full Term Day 3</td>
<td>1.7 - 14</td>
</tr>
<tr>
<td>Full Term Day 7</td>
<td>2.0 - 11</td>
</tr>
<tr>
<td>31d - 11m</td>
<td>2.8 - 23</td>
</tr>
<tr>
<td>12m - 15y (8:00 AM)</td>
<td>3.0 - 21</td>
</tr>
</tbody>
</table>

Adults

8:00 AM 8.0 - 19
4:00 PM 4.0 - 11

Deoxycorticosterone (DOC)

Units: ng/dL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26 - 28w) Day 4</td>
<td>20 - 105</td>
</tr>
<tr>
<td>Premature (34 - 36w) Day 4</td>
<td>28 - 78</td>
</tr>
</tbody>
</table>

Newborn: Levels are markedly elevated at birth and decrease rapidly during the first week to the range of 7 - 49 as found in older infants.

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 11m</td>
<td>7 - 49</td>
</tr>
<tr>
<td>Prepubertal Children</td>
<td>2 - 34</td>
</tr>
<tr>
<td>Pubertal Children and Adults 8:00 AM</td>
<td>2 - 19</td>
</tr>
</tbody>
</table>

Dehydroepiandrosterone (DHEA)

Units: ng/dL
<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26 - 31w)</td>
<td>82 - 1484</td>
</tr>
<tr>
<td>Premature (32 - 35w)</td>
<td>56 - 1853</td>
</tr>
<tr>
<td>Full Term (2 - 7d)</td>
<td>41 - 1292</td>
</tr>
<tr>
<td>8d - 5m</td>
<td></td>
</tr>
<tr>
<td>6 - 12m</td>
<td></td>
</tr>
<tr>
<td>1 - 5 y</td>
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<td>6 - 7 y</td>
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<td>8 - 10 y</td>
<td></td>
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<tr>
<td>11 - 12 y</td>
<td></td>
</tr>
<tr>
<td>13 - 14 y</td>
<td></td>
</tr>
<tr>
<td>15 - 16 y</td>
<td>39 - 481</td>
</tr>
<tr>
<td>17 - 19 y</td>
<td>40 - 491</td>
</tr>
<tr>
<td>20 - 49 y</td>
<td>31 - 701</td>
</tr>
<tr>
<td>&gt; or = 50 y</td>
<td>21 - 402</td>
</tr>
</tbody>
</table>

11-Desoxycortisol

Units: ng/dL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>110 - 1376</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
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<tr>
<td>Newborn Day 3</td>
<td>13 - 147</td>
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<tr>
<td>1 - 11m</td>
<td>156</td>
</tr>
<tr>
<td>Prepubertal 8:00 AM</td>
<td>20 - 155</td>
</tr>
<tr>
<td>Pubertal Children and Adults 8:00 AM</td>
<td>12 - 158</td>
</tr>
</tbody>
</table>

17-OH Pregnenolone

Units: ng/dL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>375 - 3559</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>64 - 2380</td>
</tr>
<tr>
<td>3 Days</td>
<td>10 - 829</td>
</tr>
<tr>
<td>1 - 5m</td>
<td>36 - 763</td>
</tr>
<tr>
<td>6 - 11m</td>
<td>42 - 540</td>
</tr>
<tr>
<td>12 - 23m</td>
<td>14 - 207</td>
</tr>
<tr>
<td>24m - 5y</td>
<td>10 - 103</td>
</tr>
<tr>
<td>6 - 9y</td>
<td>10 - 186</td>
</tr>
<tr>
<td>Pubertal</td>
<td>44 - 235</td>
</tr>
<tr>
<td>Adults</td>
<td>53 - 357</td>
</tr>
</tbody>
</table>

Progesterone
Units: ng/dL

### Males

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 16y</td>
<td>15</td>
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<tr>
<td>Adults</td>
<td>11</td>
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### Females

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>1-10y</td>
<td>26</td>
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<tr>
<td>11y</td>
<td>255</td>
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<tr>
<td>12y</td>
<td>856</td>
</tr>
<tr>
<td>13y</td>
<td>693</td>
</tr>
<tr>
<td>14y</td>
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<tr>
<td>15y</td>
<td>1076</td>
</tr>
<tr>
<td>16y</td>
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</table>

### Adult

<table>
<thead>
<tr>
<th>Cycle Days</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 6</td>
<td>17</td>
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<tr>
<td>7 - 12</td>
<td>135</td>
</tr>
<tr>
<td>13 - 15</td>
<td>1563</td>
</tr>
<tr>
<td>16 - 28</td>
<td>2555</td>
</tr>
</tbody>
</table>

### Post Menopausal

Note: Luteal progesterone peaked from 350 to 3750 ng/dL on days ranging from 17 to 23.

17-Alpha-Hydroxyprogesterone 17-OHP

Units: ng/dL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>124 - 841</td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>26 - 568</td>
</tr>
<tr>
<td>Full-Term Day 3</td>
<td></td>
</tr>
</tbody>
</table>

Males: Levels increase after the first week to peak values ranging from 40 - 200 between 30 and 60 days. Values then decline to a prepubertal value of one year.

### Prepubertal

<table>
<thead>
<tr>
<th>Adult Males</th>
<th></th>
</tr>
</thead>
</table>

### Females
<table>
<thead>
<tr>
<th>Age Range</th>
<th>Prepubertal Males and Females</th>
<th>Adult Males &gt;18 years</th>
<th>Adult Females</th>
<th>Prepubertal Females</th>
<th>Postmenopausal Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 - 106</td>
<td></td>
<td>264 - 916</td>
<td>10</td>
<td>5 - 16</td>
<td>5 - 22</td>
</tr>
<tr>
<td>Adult Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular 15-70</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luteal 35-290</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Testosterone, Total</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Units: ng/dL</td>
<td>Age Range</td>
<td>Males</td>
<td>Females</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature (26-28w) Day 4</td>
<td>59 - 125</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature (31-35w) Day 4</td>
<td>37 - 198</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newborns</td>
<td>75 - 400</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 - 7m: Levels decrease rapidly the first week to 20 - 50, then increase to 60 - 400 between 20 - 60 days. Levels then decline to prepubertal range levels of 10 by seven months.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 - 7m: Levels decrease during the first month to less than 10 and remain there until puberty.</td>
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<td></td>
</tr>
</tbody>
</table>
Congenital Adrenal Hyperplasia (CAH) Profile for 21-Hydroxylase Deficiency

Clinical Information: The cause of congenital adrenal hyperplasia (CAH) is an inherited genetic defect that results in decreased formation of 1 of the many enzymes that are involved in the production of cortisol. The enzyme defect results in reduced glucocorticoids and mineralocorticoids, and elevated 17-hydroxyprogesterone (OHPG) and androgens. The resulting hormone imbalances can lead to life-threatening, salt-wasting crises in the newborn period and incorrect gender assignment of virilized females. Adult-onset CAH may result in hirsutism or infertility in females. The adrenal glands, ovaries, testes, and placenta produce OHPG. It is hydroxylated at the 11 and 21 positions to produce cortisol. Deficiency of either 11- or 21-hydroxylase results in decreased cortisol synthesis, and the feedback inhibition of adrenocorticotropic hormone (ACTH) secretion is lost. Consequently, increased pituitary release of ACTH increases production of OHPG. In contrast, if 17-alpha-hydroxylase (which allows formation of OHPG from progesterone) or 3-beta-ol-dehydrogenase (which allows formation of 17-hydroxyprogesterone formation from 17-hydroxypregnenolone) are deficient, OHPG levels are low with possible increase in progesterone or pregnenolone, respectively. Most (90%) cases of CAH are due to mutations in the 21-hydroxylase gene (CYP21A2). CAH due to 21-hydroxylase deficiency is diagnosed by confirming elevations of OHPG and androstenedione with decreased cortisol. By contrast, in 2 less common forms of CAH, due to 17-hydroxylase or 11-hydroxylase deficiency, OHPG and androstenedione levels are not significantly elevated and measurement of progesterone (PGSN / Progesterone, Serum) and deoxycorticosterone (DCRN / 11-Deoxycorticosterone, Serum), respectively, are necessary for diagnosis. OHPG is bound to both transcortin and albumin, and total OHPG is measured in this assay. OHPG is converted to pregnanetriol, which is conjugated and excreted in the urine. In all instances, more specific tests than pregnanetriol measurement are available to diagnose disorders of steroid metabolism. The CAH profile allows the simultaneous determination of OHPG, androstenedione, and cortisol. These steroids can also be ordered individually (OHPG / 17-Hydroxyprogesterone, Serum; ANST / Androstenedione, Serum; CINP / Cortisol, Serum, LC-MS/MS).

Useful For: Preferred screening test for congenital adrenal hyperplasia (CAH) that is caused by 21-hydroxylase deficiency Part of a battery of tests to evaluate females with hirsutism or infertility, which can result from adult-onset CAH

Interpretation: Diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always requires the measurement of several steroids. Patients with CAH due to 21-hydroxylase gene (CYP21A2) mutations usually have very high levels of androstenedione, often 5- to 10-fold elevations. 17-Hydroxyprogesterone (OHPG) levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. In the much less common CYP11A mutation, androstenedione levels are elevated to a similar extent as in CYP21A2 mutation, and cortisol is also low, but OHPG is only mildly, if at all, elevated. Also less common is 3 beta-hydroxysteroid dehydrogenase type 2 (3 beta HSD-2) deficiency, characterized by low cortisol and substantial elevations in dehydroepiandrosterone sulfate (DHEA-S) and 17-alpha-hydroxyprogrenolone, while androstenedione is either low, normal, or rarely, very mildly elevated (as a consequence of peripheral tissue androstenedione production by 3 beta HSD-1). In the very rare steroidogenic acute regulatory protein deficiency, all steroid hormone levels are low and cholesterol is elevated. In the also very rare 17-alpha-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxyprogrenolone, OHPG, DHEA-S), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid.
and its precursors, in particular progesterone, 11-deoxycorticosterone, corticosterone, and 18-hydroxycorticosterone, are increased. The goal of CAH treatment is normalization of cortisol levels and, ideally, also of sex-steroid levels. OHPG is measured to guide treatment, but this test correlates only modestly with androgen levels. Therefore, androstenedione and testosterone should also be measured and used to guide treatment modifications. Normal prepubertal levels may be difficult to achieve, but if testosterone levels are within the reference range, androstenedione levels up to 100 ng/dL are usually regarded as acceptable.

**Reference Values:**

<table>
<thead>
<tr>
<th>Tanner Stages</th>
<th>Age (Years)</th>
<th>Reference Range (ng/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (prepubertal)</td>
<td>9.8-14.5</td>
<td>31-65</td>
</tr>
<tr>
<td>Stage II</td>
<td>10.7-15.4</td>
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<tr>
<td>Stage III</td>
<td>11.8-16.2</td>
<td>48-140</td>
</tr>
<tr>
<td>Stage IV</td>
<td>12.8-17.3</td>
<td>65-210 Females*</td>
</tr>
</tbody>
</table>

*Tanner Stages Age (Years) Reference Range (ng/dL)

<table>
<thead>
<tr>
<th>Tanner Stages</th>
<th>Age (Years)</th>
<th>Reference Range (ng/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (prepubertal)</td>
<td>9.2-13.7</td>
<td>42-100</td>
</tr>
<tr>
<td>Stage II</td>
<td>10.0-14.4</td>
<td>80-190</td>
</tr>
<tr>
<td>Stage III</td>
<td>10.7-15.6</td>
<td>77-225</td>
</tr>
<tr>
<td>Stage IV</td>
<td>11.8-18.6</td>
<td>80-240</td>
</tr>
</tbody>
</table>


17-HYDROXYPROGESTERONE

 Children Preterm infants: Preterm infants may exceed 630 ng/dL, however, it is uncommon to see levels reach 1,000 ng/dL. Term infants 0-28 days: Levels fall from newborn (to prepubertal gradually within 6 months. Prepubertal males: Prepubertal females: Adults Males: Females Follicular: Luteal: Postmenopausal: Note: For pregnancy reference ranges, see: Soldin OP, Guo T, Weiderpass E, et al: Steroid hormone levels in pregnancy and 1 year postpartum using isotope dilution tandem mass spectrometry. Fertil Steril 2005 Sept;84(3):701-710

**Clinical References:**


**NGCDA**

**Congenital Dyserythropoietic Anemia Sequencing, Varies**

**Clinical Information:** Next-generation sequencing (NGS) is a methodology that can interrogate large regions of genomic DNA in a single assay. The presence and pattern of gene mutations can provide critical diagnostic, prognostic, and therapeutic information for managing physicians. This panel
aids in the diagnosis and genetic counseling of individuals with clinical or familial features of congenital dyserythropoietic anemia (CDA). CDA is a disorder of ineffective erythropoiesis clinically subdivided into subtypes with various phenotypic findings that segregate into different gene associations.(1-4) These disorders have distinctive cytopathologic findings consisting of nuclear abnormalities in bone marrow erythroid precursors. Types I and II CDA are inherited in an autosomal recessive pattern whereas types III and IV are autosomal dominant.

**Useful For:** Confirmation of the diagnosis or carrier mutation status of genes associated with congenital dyserythropoietic anemia Identifying mutations within genes associated with phenotypic severity, allowing for predictive testing and further genetic counseling

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(5,6) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Neutropenia is identified but not as the main finding. Pathogenic variants in ELANE, which encodes neutrophil elastase, can result in severe congenital neutropenia type 1 (SCN1) or cyclic neutropenia. SCN1 often presents immediately with omphalitis, while diarrhea, pneumonia, and deep abscesses affecting the liver, lungs, or subcutaneous tissues are noted within the first year. Patients are at risk for development of myelodysplastic syndrome or acute myelogenous leukemia, presumably due to acquired mutations in CSF3R (which may also be identified in the presence of congenital neutropenia due to variants in genes other than ELANE, see below). Biallelic mutations in CSF3R have also been recently reported to be associated with severe congenital neutropenia. Cyclic neutropenia typically presents in the first year of life with 3-week-long oscillations in cell counts along with intervals of fever, oral ulcerations, and ulcerations; between intervals, patients are generally healthy. Unlike SCN1, cyclic neutropenia is not associated with risk of malignancy. Both SCN1 and cyclic neutropenia are inherited in an autosomal dominant pattern from an affected parent, although de novo mutations have been identified. Studies have demonstrated pathogenic variants in ELANE in nearly 100% of cases with well-documented classical cyclic neutropenia, while in some cases with atypical presentations (ie, oscillations that are not 3 weeks) a variant in ELANE is not identified. ELANE variants are identified in 38% to 80% of cases of congenital neutropenia, depending on the criteria used to identify patients. Although there is some overlap, generally, variants at the active site of neutrophil elastase result in cyclic neutropenia, while variants that prevent normal folding or packaging of the enzyme cause congenital neutropenia. In addition to variants in ELANE, severe congenital neutropenia where the predominant finding is neutropenia can be inherited as a result of pathogenic variants in other genes. Dominant variants in GF11 (encoding growth factor independent 1) result in severe congenital neutropenia type 2 (SCN2). Pathogenic variants in G6PC3 (encoding glucose-6-phosphate 3), which are inherited in an autosomal recessive manner, can result in a phenotypic spectrum from isolated nonsyndromic severe congenital neutropenia to classic G6PC3 deficiency (severe neutropenia along with cardiovascular and urogenital abnormalities) to severe G6PC3 deficiency (also known as Dursun syndrome, which includes features of classic G6PC3 deficiency along with severe lymphopenia, primary pulmonary hypertension, thymic hypoplasia, among other features). Kostmann disease or severe congenital neutropenia type 3 (SCN3) is due to recessive inheritance of pathogenic variants in HAX1 (which encodes HCLS1-associated protein X-1) and may result in seizures and developmental delay in addition to neutropenia. Along with neutropenia, variants in VPS45 inherited in an autosomal recessive manner (also known as severe congenital neutropenia type 5 [SCN5]) are associated with neutrophil dysfunction, bone marrow fibrosis, and nephromegaly due to renal extramedullary hematopoiesis. While loss-of-function variants in WAS, which is located on the X chromosome, cause Wiskott-Aldrich syndrome (characterized by thrombocytopenia, eczema, and recurrent infections), gain-of-function variants affecting the autoinhibitory structure of the protein, have been associated with congenital neutropenia, along with variable lymphopenia, decreased lymphocyte proliferation, and impaired phagocyte activity. Pathogenic variants in WIPF1 can present with similar findings to Wiskott-Aldrich syndrome. Severe neutropenia may also be present as part of a multisystem disorder. Barth syndrome, due to pathogenic variants in TAZ, which is located on the X-chromosome, is characterized by neutropenia, cardio- and skeletal myopathy, growth delay, and distinctive facial features. Biallelic variants in C16orf57 manifest as poikiloderma with neutropenia; the neutropenia may be cyclical. In Cohen syndrome, an autosomal recessive disorder due to variants in COH1 (also known as VPS13B), neutropenia is accompanied by hypotonia, developmental delays, microcephaly, failure to thrive in infancy, truncal obesity in adolescent years, ophthalmologic findings, joint hypermobility, a cheerful disposition, and characteristic facial features. Glycogen storage disease type I (GSDI), caused by biallelic pathogenic variants in either G6PC or SLC37A4, when untreated can result in chronic neutropenia and impaired neutrophil and monocyte function, as well as the characteristic findings that include accumulation of glycogen and fat in the liver and kidneys. Pathogenic variants in LAMTOR2/MAPBP1P have been shown to result in neutropenia, decreased cytotoxic activity of CD8+ T-cells, short stature, and hypopigmented skin. Persistent or intermittent neutropenia is often a presenting feature of Shwachman-Diamond syndrome (SDS), which is also characterized by exocrine pancreatic dysfunction (with malabsorption, malnutrition, and growth failure), bone abnormalities, and hematologic abnormalities (single- or multilineage cytopenias along with predisposition to myelodysplastic syndrome and acute myelogenous leukemia). SDS is an autosomal recessive disorder due to pathogenic variants in SBDS. Warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis (WHIM) syndrome is characterized by neutropenia in addition to hypogammaglobulinemia, and susceptibility to human papillomavirus. It is due to autosomal dominant pathogenic variants in CXCR4. Although most forms of Hermansky-Pudlak syndrome do not include significant neutropenia, type 2 caused by variants in AP3B1 can be associated with persistent neutropenia and increased infections in addition to the typical findings of
tyrosinase-positive oculocutaneous albinism, platelet storage pool deficiency, pulmonary fibrosis, and granulomatous colitis. Few patients with RAC2 pathogenic variants have been identified, but neutrophil dysfunction appears to be a feature, though CD11b expression and specific granule release appear to be preserved. Both individuals with dominant and individuals with recessive inheritance have been identified, with and without additional associated phenotypic findings. GATA-binding protein (GATA2) deficiency demonstrates a wide spectrum of clinical presentations, including neutropenia. Most variants appear to arise de novo (spontaneously) and are then transmitted in an autosomal dominant manner. If the clinical phenotype strongly suggests GATA2 deficiency, this gene is available as a stand-alone test (see GATA2 / GATA-Binding Protein 2 (GATA2) Comprehensive Gene Sequencing). This panel does not evaluate for somatic (acquired) ASXL1 mutations associated with GATA2 deficiency. Table 1. Genes included in the Congenital Neutropenia/Neutrophil-Related PID Gene Panel GENE SYMBOL (ALIAS) PROTEIN OMIM INCIDENCE INHERITANCE PHENOTYPE DISORDER AP3B1 AP-3 complex subunit beta-1 isoform 1 603401 Rare AR Hermansky-Pudlak syndrome 2 CSF3R Granulocyte colony-stimulating factor receptor isoform 1 603401 Rare AR Hermansky-Pudlak syndrome 2 CSF3R Granulocyte colony-stimulating factor receptor isoform 1 603401 Rare AR Hermansky-Pudlak syndrome 2 CSF3R Granulocyte colony-stimulating factor receptor isoform 1 603401 Rare AR Hermansky-Pudlak syndrome 2 CSF3R Granulocyte colony-stimulating factor receptor isoform 1 603401 Rare AR Hermansky-Pudlak syndrome 2 CSF3R Granulocyte colony-stimulating factor receptor isoform 1 603401 Rare AR Hermansky-Pudlak syndrome 2 CSF3R Granulocyte colony-stimulating factor receptor isoform 1 603401 Rare AR Hermansky-Pudlak syndrome 2 CSF3R Granulocyte colony-stimulating factor receptor isoform 1 603401 Rare AR Hermansky-Pudlak syndrome 2 CSF3R Granulocyte 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603401 Rare AR Hermansky-Pudlak syndrome 2 CSF3R Granulocyte colony-stimulating factor receptor isoform 1 603401 Rare AR Hermansky-Pudlak syndrome 2 CSF3R Granulocyte colony-stimulating factor receptor isoform 1 603401 Rare AR Hermansky-Pudlak syndrome 2 CSF3R...
CONGR 82466

Congo Red Stain (Bill Only)

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

CTDC 83631

Connective Tissue Diseases Cascade, Serum

**Clinical Information:** The following diseases are often referred to as connective tissue diseases: rheumatoid arthritis (RA), lupus erythematosus (LE), scleroderma (systemic sclerosis) CREST syndrome (calcinoïd, Raynaud phenomenon, esophageal hypomotility, sclerodactyly, and telangiectasia), Sjögren syndrome, mixed connective tissue disease (MCTD), and polymyositis. Connective tissue diseases (systemic rheumatic diseases) are characterized by immune-mediated inflammation that involves the joints, skin, and visceral organs. These diseases are also accompanied by antibodies to a host of nuclear and cytoplasmic autoantigens. The diagnosis of a connective tissue disease is based on clinical signs and symptoms and characteristic radiographic, histopathologic, and serologic findings. Certain connective tissue diseases are characterized by autoantibodies that are highly specific for individual diseases (see table). Connective tissue diseases often present clinically with signs and symptoms that are nonspecific, including constitutional signs (e.g., fever, weight loss, fatigue, and arthralgias). Accordingly, consideration of the possibility of a connective tissue disease is common on initial clinical presentation and testing for antibodies to autoantigens associated with connective tissue diseases is often performed early in the evaluation of many patients. (1) Autoantibodies with High Specificity for Individual Connective Tissue Diseases Cyclic citrullinated peptide antibodies RA dsDNA antibodies LE Scl 70 antibodies (topoisomerase I) Scleroderma Jo 1 antibodies (histidyl tRNA synthetase) Polymyositis SSA/Ro and SSB/La antibodies Sjögren syndrome RNP antibodies (in isolation) MCTD Sm antibodies LE Ribosome P antibodies LE Centromere antibodies CREST syndrome In this test, serum is tested initially for the presence of antinuclear antibodies (ANA) and for cyclic citrullinated peptide (CCP) antibodies. The presence of CCP antibodies indicates a strong likelihood of RA. (2) The presence of ANA supports the possibility of a connective tissue disease, and the level of ANA is used to identify sera for second-order testing for antibodies to double-stranded DNA (dsDNA) and the other autoantigens. The decision threshold for performing the second-order tests is based on empirical data derived from testing patients with varying levels of ANA and was chosen to minimize testing when positive results for dsDNA and other antibodies are very unlikely. (3) The testing algorithm is useful in the initial evaluation of patients and performs best in clinical situations in which the prevalence of disease is low. (4)

**Useful For:** Evaluation of patients with signs and symptoms compatible with connective tissue
diseases

**Interpretation:** Interpretive comments are provided. See individual unit codes for additional information.

**Reference Values:**
ANTINUCLEAR ANTIBODIES (ANA)
- < or =1.0 U (negative)
- 1.1-2.9 U (weakly positive)
- 3.0-5.9 U (positive)
- > or =6.0 U (strongly positive)
Reference values apply to all ages.

CYCLIC CITRULLINATED PEPTIDE ANTIBODIES, IgG
- <20.0 U (negative)
- 20.0-39.9 U (weak positive)
- 40.0-59.9 U (positive)
- > or =60.0 U (strong positive)
Reference values apply to all ages.

**Clinical References:**

**COSPC**
Consult, Outside Slide (Bill Only)

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**CRHPC**
Consult, w/Comp Rvw of His (Bill Only)

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**CSPPC**
Consult, w/Slide Prep (Bill Only)

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**CUPPC**
Consult, w/USS Prof (Bill Only)

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.
**Conventional Smear-Diagnostic**

**Clinical Information:** Squamous cell carcinoma of the cervix is believed to develop in progressive stages from normal through precancerous (dysplastic) stages, to carcinoma in situ, and eventually invasive carcinoma. This sequence is felt to develop over a matter of years in most patients. The etiology of cervical carcinoma is unknown, but the disease is believed to be related to sexual activity and possibly sexually transmitted viral infections such as human papillomavirus (HPV). Most cervical carcinomas and precancerous conditions occur in the transformation zone (squamo-columnar junction), therefore, this area needs to be sampled if optimum results are to be obtained.

**Useful For:** Screening for cervical carcinoma and a number of infections of the female genital tract including human papillomavirus, herpes, Candida, and Trichomonas

**Interpretation:** Standard reporting, as defined by the Bethesda System (TBS) is utilized.

**Reference Values:**
Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.

Note: Abnormal results will be reviewed by a physician at an additional charge.

**Clinical References:**

**Conventional Smear-Screen**

**Clinical Information:** Squamous cell carcinoma of the cervix is believed to develop in progressive stages from normal through precancerous (dysplastic, intraepithelial neoplastic, stages II in situ carcinoma, and eventually invasive carcinoma). This sequence is felt to develop over a matter of years in most patients. The etiology of cervical carcinoma is unknown but the disease is believed to be related to sexual activity and possibly sexually transmitted viral infections such as human papilloma virus. Most cervical carcinomas and precancerous conditions occur in the transformation zone (squamo-columnar junction), therefore, this area needs to be sampled if optimum results are to be obtained.

**Useful For:** Screening for cervical carcinoma and a number of infections of the female genital tract including human papillomavirus, herpes, Candida, and Trichomonas

**Interpretation:** Standard reporting, as defined by the Bethesda System (TBS) is utilized.

**Reference Values:**
Satisfactory for evaluation
Negative for intraepithelial lesion or malignancy

Note: Abnormal results will be reviewed by a physician at an additional charge.

**Clinical References:**

**Copper, 24 Hour, Urine**

**Clinical Information:** The biliary system is the major pathway of copper excretion. Biliary excretion of copper requires an adenosine triphosphate (ATP)-dependent transporter protein. Mutations in the gene for the transporter protein cause hepatolenticular degeneration (Wilson disease).
Ceruloplasmin, the primary copper-carrying protein in the blood, is also reduced in Wilson disease. Urine copper excretion is increased in Wilson disease due to a decreased serum binding of copper to ceruloplasmin, or due to allelic variances in cellular metal ion transporters. Hypercupriuria is also found in hemochromatosis, biliary cirrhosis, thyrotoxicosis, various infections, and a variety of other acute, chronic, and malignant diseases (including leukemia). Urine copper concentrations are also elevated in patients taking contraceptives or estrogens and during pregnancy. Low urine copper levels are seen in malnutrition, hypoproteinemias, malabsorption, and nephrotic syndrome. Increased zinc consumption interferes with normal copper absorption from the gastrointestinal tract causing hypocupremia.

**Useful For:** Investigation of Wilson disease and obstructive liver disease using a 24-hour urine specimen

**Interpretation:**
Humans normally excrete less than 60 mcg/day of copper in the urine. Urinary copper excretion greater than 60 mcg/day may be seen in: -Wilson disease -Obstructive biliary disease (eg, primary biliary cirrhosis, primary sclerosing cholangitis) -Nephrotic syndrome (due to leakage through the kidney) -Chelation therapy -Estrogen therapy -Mega-dosing of zinc-containing vitamins Because ceruloplasmin is an acute phase reactant, urine copper is elevated during acute inflammation. During the recovery phase, urine copper is usually below normal, reflecting the expected physiologic response to replace the copper that was depleted during inflammation.

**Reference Values:**
0-17 years: not established
> or =18 years: < or =60 mcg/24h


**Copper, Liver Tissue**

**Clinical Information:** Homeostatic regulation of copper metabolism is very complex. The liver is the key organ to facilitate copper storage and incorporation of copper into the transport protein ceruloplasmin. Intestinal absorption and biliary excretion also play major roles in the regulation of copper homeostasis. Abnormal copper metabolism is associated with liver disease. Elevated serum copper concentrations are seen in portal cirrhosis, biliary tract disease, and hepatitis, probably because excess copper that would normally be excreted in the bile is retained in circulation. In primary biliary cirrhosis, ceruloplasmin is high, resulting in high serum copper. Lesser elevations of hepatic copper are found in chronic copper poisoning, obstructive jaundice, and certain cases of hepatic cirrhosis. Reduced serum copper concentration is typical of Wilson disease (hepatolenticular degeneration). Wilson disease is characterized by liver disease, neurologic abnormalities, and psychiatric disturbances. Kayser-Fleischer rings are normally present and urinary copper excretion is increased, while serum copper and ceruloplasmin are low.

**Useful For:** Diagnosing Wilson disease and primary biliary cirrhosis

**Interpretation:** The constellation of symptoms associated with Wilson disease (WD), which includes Kayser-Fleischer rings, behavior changes, and liver disease, is commonly associated with liver copper concentration above 250 mcg/dry weight. VERY HIGH: Above 1,000 mcg/g dry weight. This finding is virtually diagnostic of WD; such patients should be showing all the signs and symptoms of WD. HIGH: 250 mcg/g dry weight to 1,000 mcg/g dry weight. This finding is suggestive of WD unless signs and symptoms, supporting histology, and other biochemical results (low serum ceruloplasmin, low serum copper, and high urine copper) are not evident. HIGH: 35 mcg/g dry weight to 250 mcg/g dry weight. Excessive copper at this level can be associated with cholestatic liver disease, such as primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, and familial cholestatic syndrome. The heterozygous carriers for WD occasionally have modestly elevated values, but rarely higher than 125 mcg/g of dry weight. In general, the liver copper content is higher than 250 mcg/g dried tissue in WD
patients. In patients with elevated levels of copper without supporting histology and other biochemical test results, contamination during collection, handling, or processing should be considered. Fresh tissue would be appropriate for copper measurement. Genetic test for WD (WDZ / Wilson Disease, Full Gene Analysis) is available at Mayo Clinic.

**Reference Values:**

10-35 mcg/g dry weight

>1,000 mcg/g dry weight: VERY HIGH

This finding is strongly suggestive of Wilson disease. If this finding is without supporting histology and other biochemical test results, contamination during collection, handling, or processing should be considered. Fresh tissue would be appropriate for copper measurement. Genetic test for Wilson disease (WDZ / Wilson Disease, Full Gene Analysis) is also available at Mayo Clinic. Call 800-533-1710 or 507-266-5700 if you need further assistance.

250-1,000 mcg/g dry weight: HIGH

This finding is suggestive of possible Wilson disease. If this finding is without supporting histology and other biochemical test results, contamination during collection, handling, or processing should be considered. Fresh tissue would be appropriate for copper measurement. Genetic test for Wilson disease (WDZ / Wilson Disease, Full Gene Analysis) is also available at Mayo Clinic. Call 800-533-1710 or 507-266-5700 if you need further assistance.

35-250 mcg/g dry weight: HIGH

Excessive copper at this level can be associated with cholestatic liver disease, such as primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, and familial cholestatic syndrome. Heterozygous carriers for Wilson disease occasionally have modestly elevated values, but rarely higher than 125 mcg/g of dry weight. In general, the liver copper content is higher than 250 mcg/g dried tissue in patients with Wilson disease. If this finding is without supporting histology and other biochemical test results, contamination during collection, handling, or processing should be considered. Fresh tissue would be appropriate for copper measurement. Genetic test for Wilson disease (WDZ / Wilson Disease, Full Gene Analysis) is also available at Mayo Clinic. Call 800-533-1710 or 507-266-5700 if you need further assistance.

**Clinical References:**


**Copper, Serum**

**Clinical Information:** In serum from normal, healthy humans, more than 95% of the copper is incorporated into ceruloplasmin; the remaining copper is loosely bound to albumin. Low serum copper, most often due to excess iron or zinc ingestion and infrequently due to dietary copper deficit, results in severe derangement in growth and impaired erythropoiesis. Low serum copper is also observed in hepatotencular degeneration (Wilson disease) due to a decrease in the synthesis of ceruloplasmin and allelic variances in cellular metal ion transporters. In Wilson disease, the albumin-bound copper may actually be increased, but ceruloplasmin copper is low, resulting in low serum copper. However, during the acute phase of Wilson disease (fulminant hepatic failure), ceruloplasmin and copper may be normal; in this circumstance, hepatic inflammation causes increased release of ceruloplasmin. It is useful to relate the degree of liver inflammation to the ceruloplasmin and copper-see discussion on hypercupremia below. Significant hepatic inflammation with normal ceruloplasmin and copper suggest acute Wilson disease. Other disorders associated with decreased serum copper concentrations include malnutrition, hypoproteinemia, malabsorption, nephrotic syndrome, Menkes disease, copper toxicity,
and megadosing of zinc-containing vitamins (zinc interferes with normal copper absorption from the gastrointestinal tract). Hypercupremia is found in primary biliary cirrhosis, primary sclerosing cholangitis, hemochromatosis, malignant diseases (including leukemia), thyrotoxicosis, and various infections. Serum copper concentrations are also elevated in patients taking contraceptives or estrogens and during pregnancy. Since the gastrointestinal (GI) tract effectively excludes excess copper, it is the GI tract that is most affected by copper ingestion. Increased serum concentration does not, by itself, indicate copper toxicity.

**Useful For:** Diagnosis of: - Wilson disease - Primary biliary cirrhosis - Primary sclerosing cholangitis

**Interpretation:** Serum copper below the normal range is associated with Wilson disease, as well as a variety of other clinical situations (see Clinical Information). Excess use of denture cream containing zinc can cause hypocupremia. Serum concentrations above the normal range are seen in primary biliary cirrhosis and primary sclerosing cholangitis, as well as a variety of other clinical situations (see Clinical Information).

**Reference Values:**

- 0-2 months: 0.40-1.40 mcg/mL
- 3-6 months: 0.40-1.60 mcg/mL
- 7-9 months: 0.40-1.70 mcg/mL
- 10-12 months: 0.80-1.70 mcg/mL
- 13 months-10 years: 0.80-1.70 mcg/mL
- > or =11 years: 0.75-1.45 mcg/mL

**Clinical References:**
2. Wiesner RH, LaRusso NF, Ludwig J, Dickson ER: Comparison of the clinicopathologic features of primary sclerosing cholangitis and primary biliary cirrhosis. Gastroenterology 1985;88:108-114

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**Copper/Creatinine Ratio, Random, Urine**


**Useful For:** Investigation of Wilson disease and obstructive liver disease using a random urine specimen

**Interpretation:** Humans normally excrete less than 60 mcg/24 hour in the urine. Urinary copper excretion greater than 60 mcg/24 hour may be seen in: - Wilson disease - Obstructive biliary disease (eg, primary biliary cirrhosis, primary sclerosing cholangitis) - Nephrotic syndrome (due to leakage through the kidney) - Chelation therapy - Estrogen therapy - Mega-dosing of zinc-containing vitamins Because ceruloplasmin is an acute phase reactant, urine copper is elevated during acute inflammation. During the recovery phase, urine copper is usually below normal, reflecting the expected physiologic response to replace the copper that was depleted during inflammation.
Reference Values:
0-17 years: not established
Male >or =18 years: 9-43 mcg/g creatinine
Female >or =18 years: 7-72 mcg/g creatinine


Coriander, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 >or =100 Strongly positive Reference values apply to all ages.

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation* 2.0 Upper Limit of Quantitation** 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Corn IgG4**

**Interpretation:** mcg/mL of IgG4 Lower Limit of Quantitation 0.15 Upper Limit of Quantitation 30.0

**Reference Values:**

<0.15 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicated immunologic sensitization to the food allergen in question.

**Corn Pollen, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
</tbody>
</table>

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
CORN 82705

Corn-Food, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
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<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or ≥100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Cortisol, Serum

Clinical Information: Cortisol is a steroid hormone and a precursor molecule for aldosterone. It is produced from deoxycorticosterone, further converted to 18-hydroxy cortisol and, finally, to aldosterone in the mineralocorticoid pathway. The adrenal glands, ovaries, testes, and placenta produce steroid hormones, which can be subdivided into 3 major groups: mineral corticoids, glucocorticoids, and sex steroids. Synthesis proceeds from cholesterol along 3 parallel pathways, corresponding to these 3 major groups of steroids, through successive side-chain cleavage and hydroxylation reactions. At various levels of each pathway, intermediate products can move into the respective adjacent pathways via additional, enzymatically catalyzed reactions (see Steroid Pathways in Special Instructions). Corticosterone is the first intermediate in the corticoid pathway with significant mineral corticoid activity. Its synthesis from 11-deoxycorticosterone is catalyzed by 11 beta-hydroxylase 2 (CYP11B2) or by 11 beta-hydroxylase 1 (CYP11B1). Corticosterone is in turn converted to 18-hydroxycorticosterone and finally to aldosterone, the most active mineral corticoid. Both of these reactions are catalyzed by CYP11B2, which, unlike its sister enzyme CYP11B1, also possesses 18-hydroxylase and 18-methyloxidase (also known as aldosterone synthase) activity. The major diagnostic utility of measurements of steroid synthesis intermediates lies in the diagnosis of disorders of steroid synthesis, in particular congenital adrenal hyperplasia (CAH). All types of CAH are associated with cortisol deficiency with the exception of CYP11B2 deficiency and isolated impairments of the 17-lyase activity of CYP17A1 (this enzyme also has 17 alpha-hydroxylase activity). In cases of severe illness or trauma, CAH predisposes patients to poor recovery or death. Patients with the most common form of CAH (21-hydroxylase deficiency, >90% of cases), with the third most common form of CAH (3-beta-steroid dehydrogenase deficiency, <3% of cases) and those with the extremely rare StAR (steriodogenic acute regulatory protein) or 20,22 desmolase deficiencies might also suffer mineral corticoid deficiency, as the enzyme blocks in these disorders are proximal to potent mineral corticoids. These patients might suffer salt-wasting crises in infancy. By contrast, patients with the second most common form of CAH, 11-hydroxylase deficiency (<5% of cases) are normotensive or hypertensive, as the block affects either CYP11B1 or CYP11B2, but rarely both, thus ensuring that at least cortisol is still produced. In addition, patients with all forms of CAH might suffer the effects of substrate accumulation proximal to the enzyme block. In the 3 most common forms of CAH, the accumulating precursors spill over into the sex steroid pathway, resulting in virilization of females or, in milder cases, hirsutism, polycystic ovarian syndrome or infertility, as well as in possible premature adrenarche and pubarche in both genders. Measurement of the various precursors of mature mineral corticoid and glucocorticoids, in concert with the determination of sex steroid concentrations, allows diagnosis of CAH and its precise type, and serves as an aid in monitoring steroid replacement therapy and other therapeutic interventions. Measurement of corticosterone is used as an adjunct to 11-deoxycorticosterone and 11-deoxycortisol (also known as compound S) measurement in the diagnosis of: -CYP11B1 deficiency (associated with cortisol deficiency) -The less common CYP11B2 deficiency (no cortisol deficiency) -The rare glucocorticoid responsive hyperaldosteronism (where expression of the gene CYP11B2 is driven by the CYP11B1 promoter, thus making it responsive to adrenocorticotrophic hormone: ACTH rather than renin) -Isolated loss of function of the 18-hydroxylase or 18-methyloxidase activity of CYP11B2 For other forms of CAH, the following tests might be relevant: -21-Hydroxylase deficiency: - OHPG / 17-Hydroxyprogesterone, Serum - ANST / Androstenedione, Serum - 21DOC / 21-Deoxycortisol, Serum -3-Beta-steroid dehydrogenase deficiency: - 17PRN / Pregnenolone and 17-Hydroxyprogrenenolone -17-Hydroxylase deficiency or 17-lyase deficiency (CYP17A1 has both activities): - 17PRN / Pregnenolone and 17-Hydroxyprogrenenolone - PGSN / Progesterone, Serum - OHPG / 17-Hydroxyprogesterone, Serum - DHEA_ / Dehydroepiandrosterone (DHEA), Serum - ANST / Androstenedione, Serum - Cortisol should be measured in all cases of suspected CAH. When evaluating for suspected 11-hydroxylase deficiency, this test should be used in conjunction with measurements of 11-deoxycortisol, 11-corticoestrone, 18-hydroxycorticosterone, cortisol, renin, and aldosterone. When evaluating congenital adrenal hyperplasia newborn screen-positive children, this test should be used in conjunction with 11-deoxycortisol and 11-deoxycorticosterone measurements as an adjunct to 17-hydroxyprogesterone, aldosterone and cortisol measurements.

Useful For: Diagnosis of suspected 11-hydroxylase deficiency, including the differential diagnosis of 11 beta-hydroxylase 1 (CYP11B1) versus 11 beta-hydroxylase 2 (CYP11B2) deficiency, and the
diagnosis of glucocorticoid-responsive hyperaldosteronism Evaluating congenital adrenal hyperplasia newborn screen-positive children, when elevations of 17-hydroxyprogesterone are only moderate, thereby suggesting possible 11-hydroxylase deficiency

**Interpretation:** In 11 beta-hydroxylase 1 (CYP11B1) deficiency, serum concentrations of cortisol will be low (usually <7 microgram/dL for a morning draw). 11-Deoxycortisol and 11-deoxycorticosterone are elevated, usually to at least 2 to 3 times (more typically 20 to 300 times) the upper limit of the normal reference range on a morning blood draw. Elevations in 11-deoxycorticosterone are usually relatively greater than those of 11-deoxycorticosterone because of the presence of intact 11 beta-hydroxylase 2 (CYP11B2). For this reason, serum concentrations of all potent mineral corticoids (corticosterone, 18-hydroxycorticosterone, and aldosterone) are typically increased above the normal reference range. Plasma renin activity is correspondingly low or completely suppressed. Caution needs to be exercised in interpreting the mineral corticoid results in infants younger than 7 days; mineral corticoid levels are often substantially elevated in healthy newborns in the first few hours of life and only decline to near-adult levels by week 1. Mild cases of CYP11B1 deficiency might require adrenocorticotropic hormone (ACTH)1-24 stimulation testing for definitive diagnosis. In affected individuals, the observed serum 11-deoxycortisol concentration 60 minutes after intravenous or intramuscular administration of 250 microgram of ACTH1-24 will usually exceed 20 ng/mL, or at least a 4-fold rise. Such increments are rarely, if ever, observed in unaffected individuals. The corresponding cortisol response will be blunted (<18 ng/mL peak). In CYP11B2 deficiency, serum cortisol concentrations are usually normal, including a normal response to ACTH1-24. 11-Deoxycorticosterone will be elevated, often more profoundly than in CYP11B1 deficiency, while 11-deoxycortisol may or may not be significantly elevated. Serum corticosterone concentrations can be low, normal, or slightly elevated, while serum 18-hydroxycorticosterone and aldosterone concentrations will be low in the majority of cases. However, if the underlying genetic defect has selectively affected 18-hydroxylase activity, corticosterone concentrations will be substantially elevated. Conversely, if the deficit affects aldosterone synthase function primarily, 18-hydroxycorticosterone concentrations will be very high. Expression of the CYP11B2 gene is normally regulated by renin and not ACTH. In glucocorticoid-responsive hyperaldosteronism, the ACTH-responsive promoter of CYP11B1 exerts aberrant control over CYP11B2 gene expression. Consequently, corticosterone, 18-hydroxycorticosterone, and aldosterone are significantly elevated in these patients and their levels follow a diurnal pattern, governed by the rhythm of ACTH secretion. In addition, the high levels of CYP11B2 lead to 18-hydroxylation of 11-deoxycortisol (an event that is ordinarily rare, as CYP11B1, which has much greater activity in 11-deoxycortisol conversion than CYP11B2, lacks 18-hydroxylation activity). Consequently, significant levels of 18-hydroxycortisol, which normally is only present in trace amounts, might be detected in these patients. Ultimate diagnostic confirmation comes from showing directly responsiveness of mineral corticoid production to ACTH1-24 injection. Normally, this has little, if any, effect on corticosterone, 18-hydroxycorticosterone, and aldosterone levels. This testing may then be further supplemented by showing that mineral corticoid levels fall after administration of dexamethasone. Sex steroid levels are moderately to significantly elevated in CYP11B1 deficiency and much less, or minimally, pronounced, in CYP11B2 deficiency. Sex steroid levels in glucocorticoid-responsive hyperaldosteronism are usually normal. Most untreated patients with 21-hydroxylase deficiency have serum 17-hydroxyprogesterone concentrations well in excess of 1,000 ng/dL. For the few patients with levels in the range of greater than 630 ng/dL, it might be prudent to consider 11-hydroxylase deficiency as an alternative diagnosis. This is particularly true if serum androstenedione concentrations are also only mildly to modestly elevated, and if the phenotype is not salt wasting but either simple virilizing (female) or normal (female or male). 11-Hydroxylase deficiency, in particular if it affects CYP11B1, can be associated with modest elevations in serum 17-hydroxyprogesterone concentrations. In these cases, testing for CYP11B1 deficiency and CYP11B2 deficiency should be considered and interpreted as described above. Alternatively, measurement of 21-deoxycortisol might be useful in these cases. This minor pathway metabolite accumulates in CYP21A2 deficiency, as it requires 21-hydroxylation to be converted to cortisol, but is usually not elevated in CYP11B1 deficiency, since its synthesis requires 11-hydroxylation of 17-hydroxyprogesterone.

**Reference Values:**

- < or =18 years: 18-1,970 ng/dL
- >18 years: 53-1,560 ng/dL
CORTO 65484

Cortisol, Free and Total, Serum

Clinical Information: Cortisol, the main glucocorticoid (representing 75%-95% of the plasma corticoids), plays a critical role in glucose metabolism and in the body's response to stress. Both hypercortisolism (Cushing disease) and hypocortisolism (Addison disease) can cause disease. Cortisol is also used to treat skin disease, allergic disorders, respiratory system disease, inflammatory disorders, and nephrotic syndrome. Cortisol levels are regulated by adrenocorticotropic hormone (ACTH), which is synthesized by the pituitary in response to corticotropin-releasing hormone (CRH). CRH is released in a cyclic fashion by the hypothalamus, resulting in diurnal peaks (6-8 a.m.) and nadirs (11 p.m.) in plasma ACTH and cortisol levels. The majority of cortisol circulates bound to corticosteroid-binding globulin (CBG) and albumin. Normally, less than 5% of circulating cortisol is free (unbound). Only free cortisol can access the enzyme transporters in liver, kidney, and other tissues that mediate metabolic and excretory clearance. Historically, measurements of free cortisol have been achieved from indirect means using a ratio known as the free cortisol index. This measurement takes into account the amount of total cortisol and CBG to give a percentage and, ultimately, absolute value of free cortisol. These methods do not take into account the variations in albumin levels. These calculations also rely on CBG, which can be lowered in critically ill patients despite normal adrenal function. Equilibrium dialysis best serves to separate free from bound cortisol without disrupting the bound fraction. Pathological hypercortisolism due to endogenous or exogenous glucocorticoids is termed Cushing syndrome. Signs and symptoms of pathological hypercortisolism may include central obesity, hypertension, hyperglycemia, hirsutism, muscle weakness, and osteoporosis. However, these symptoms and signs are not specific for pathological hypercortisolism. The majority of individuals with some or all of the symptoms and signs will not suffer from Cushing syndrome. When Cushing syndrome is present, the most common cause is iatrogenic, due to repeated or prolonged administration of, mostly, synthetic corticosteroids. Spontaneous Cushing syndrome is less common and results from either primary adrenal disease (adenoma, carcinoma, or nodular hyperplasia) or an excess of ACTH (from a pituitary tumor or an ectopic source). ACTH-dependent Cushing syndrome due to a pituitary corticotroph adenoma is the most frequently diagnosed subtype, most commonly seen in women in the third through fifth decades of life. The onset is insidious and usually occurs 2 to 5 years before a clinical diagnosis is made. Hypocortisolism most commonly presents with nonspecific lassitude, weakness, hypotension, and weight loss. Depending on the cause, hyperpigmentation may be present. More advanced cases and patients submitted to physical stress (ie, infection, spontaneous or surgical trauma) also may present with abdominal pain, hypotension, and hyperpigmentation. In extreme cases, cardiovascular shock and renal failure. The more common causes of hypocortisolism are: Primary adrenal insufficiency: Addison disease, Congenital adrenal hyperplasia, defects in enzymes involved in cortisol synthesis Secondary adrenal insufficiency: Prior, prolonged corticosteroid therapy, Pituitary insufficiency, Hypothalamic insufficiency. See Steroid Pathways in Special Instructions.

Useful For: Assessment of cortisol status in cases where there is known or a suspected abnormality in cortisol-binding proteins or albumin. Assessment of adrenal function in the critically ill or stressed patient, thus preventing unnecessary use of glucocorticoid therapy. Second-order testing when cortisol measurement by immunoassay (eg, CORT / Cortisol, Serum) gives results that are not consistent with clinical symptoms, or if patients are known to, or suspected of, taking exogenous synthetic steroids. An adjunct in the differential diagnosis of primary and secondary adrenal insufficiency. An adjunct in the differential diagnosis of Cushing syndrome.
Interpretation: Cortisol is converted to cortisone in human kidneys and cortisone is less active toward the mineralcorticoid receptor. The conversion of cortisol to cortisone in the kidney is mediated by 11B-hydroxysteroid dehydrogenase isoform-2. Also, cortisol renal clearance will be reduced when there is a deficiency in the cytochrome P450 3A5 (CYP3A5) enzyme as well as a deficiency in P-glycoprotein. Cortisol-binding globulin (CBG) has a low capacity and high affinity for cortisol, whereas albumin has a high capacity and low affinity for binding cortisol. Variations in CBG and serum albumin due to renal or liver disease may have a major impact on free cortisol. Based on the study by Bancos,(1) normal ranges of free cortisol found in patients without adrenal insufficiency were: -Free cortisol at baseline: median 0.400 mcg/dL (interquartile range: IQR 2.5-97.5% - 0.110-1.425 mcg/dL) -Free cortisol at 30 minutes: median 1.355 mcg/dL (IQR 2.5-97.5% - 0.885-2.440 mcg/dL) -Free cortisol at 60 minutes: median 1.720 mcg/dL (IQR 2.5-97.5% - 1.230-2.930 mcg/dL) Based on the study by Bancos,(1) the following cutoffs were calculated for exclusion of adrenal insufficiency: -Free cortisol at baseline*: greater than 0.271 mcg/dL (>271 ng/dL, area under the curve: AUC 0.81) -Free cortisol at 30 minutes: greater than 0.873 mcg/dL (>873 ng/dL, AUC 0.99) -Free cortisol at 60 minutes: greater than 1.190 mcg/dL (>1,190 ng/dL, AUC 0.99) (*please note that baseline free cortisol should not be used to exclude adrenal insufficiency given low performance) The use of free cortisol in the management of glucocorticoid levels in the stressed patient due to major surgery or trauma requires further studies to establish clinical dosing levels and efficacy. Cortisol pediatric reference ranges are generally the same as adults as confirmed by peer-reviewed literature.(2) In primary adrenal insufficiency, adrenocorticotrophic hormone (ACTH) levels are increased and cortisol levels are decreased; in secondary adrenal insufficiency both ACTH and cortisol levels are decreased. When symptoms of glucocorticoid deficiency are present and the 8 a.m. plasma cortisol value is less than 10 mcg/dL (or the 24-hour urinary free cortisol value is <50 mcg/24 hours), further studies are needed to establish the diagnosis. The 3 most frequently used tests are the ACTH (cosyntropin) stimulation test, the metyrapone test, and insulin-induced hypoglycemia test. First, the basal plasma ACTH concentration should be measured and the short cosyntropin stimulation test performed. Symptoms or signs of Cushing syndrome in a patient with low serum and urine cortisol levels suggest possible exogenous synthetic steroid effects.

Reference Values:
FREE CORTISOL
6-10:30 a.m. Collection: 0.121-1.065 mcg/dL.

TOTAL CORTISOL
a.m: 5-25 mcg/dL
p.m.: 2-14 mcg/dL


CORTU 8546 Cortisol, Free, 24 Hour, Urine
Clinical Information: Cortisol is a steroid hormone synthesized from cholesterol by a multienzyme cascade in the adrenal glands. It is the main glucocorticoid in humans and acts as a gene transcription factor influencing a multitude of cellular responses in virtually all tissues. Cortisol plays a critical role in glucose metabolism, maintenance of vascular tone, immune response regulation, and in the body's
response to stress. Its production is under hypothalamic-pituitary feedback control. Only a small percentage of circulating cortisol is biologically active (free), with the majority of cortisol inactive (protein bound). As plasma cortisol values increase, free cortisol (ie, unconjugated cortisol or hydrocortisone) increases and is filtered through the glomerulus. Urinary free cortisol (UFC) in the urine correlates well with the concentration of plasma free cortisol. UFC represents excretion of the circulating, biologically active, free cortisol that is responsible for the signs and symptoms of hypercortisolism. UFC is a sensitive test for the various types of adrenocortical dysfunction, particularly hypercortisolism (Cushing syndrome). A measurement of 24-hour UFC excretion, by liquid chromatography-tandem mass spectrometry (LC-MS/MS), is the preferred screening test for Cushing syndrome. LC-MS/MS methodology eliminates analytical interferences including carbamazepine (Tegretol) and synthetic corticosteroids, which can affect immunoassay-based cortisol results.

**Useful For:** Preferred screening test for Cushing syndrome Diagnosis of pseudo-hyperaldosteronism due to excessive licorice consumption This test has limited usefulness in the evaluation of adrenal insufficiency

**Interpretation:** Most patients with Cushing syndrome have increased 24-hour urinary excretion of cortisol. Further studies, including suppression or stimulation tests, measurement of serum corticotrophin concentrations, and imaging are usually necessary to confirm the diagnosis and determine the etiology. Values in the normal range may occur in patients with mild Cushing syndrome or with periodic hormonogenesis. In these cases, continuing follow-up and repeat testing are necessary to confirm the diagnosis. Patients with Cushing syndrome due to intake of synthetic glucocorticoids should have suppressed cortisol. In these circumstances a synthetic glucocorticoid screen might be ordered (SGSU / Synthetic Glucocorticoid Screen, Urine). Suppressed cortisol values may also be observed in primary adrenal insufficiency and hypopituitarism. However, many normal individuals may also exhibit a very low 24-hour urinary cortisol excretion with considerable overlap with the values observed in pathological hypocorticalism. Therefore, without other tests, 24-hour urinary cortisol measurements cannot be relied upon for the diagnosis of hypocorticalism.

**Reference Values:**
0-2 years: not established  
3-8 years: 1.4-20 mcg/24 hours  
9-12 years: 2.6-37 mcg/24 hours  
13-17 years: 4.0-56 mcg/24 hours  
> or =18 years: 3.5-45 mcg/24 hours

Use the factor below to convert from mcg/24 hours to nmol/24 hours:

**Conversion factor**  
Cortisol: mcg/24 hours x 2.76=nmol/24 hours (molecular weight=362.5)

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.

**Clinical References:**  

**Clinical Information:** Cortisol is a steroid hormone synthesized from cholesterol by a multienzyme cascade in the adrenal glands. It is the main glucocorticoid in humans and acts as a gene transcription factor influencing a multitude of cellular responses in virtually all tissues. Cortisol plays a critical role in glucose metabolism, maintenance of vascular tone, immune response regulation, and in the body's response to stress. Its production is under hypothalamic-pituitary feedback control. Only a small percentage of circulating cortisol is biologically active (free), with the majority of cortisol inactive.
As plasma cortisol values increase, free cortisol (ie, unconjugated cortisol or hydrocortisone) increases and is filtered through the glomerulus. Urinary free cortisol (UFC) correlates well with the concentration of plasma free cortisol. UFC represents excretion of the circulating, biologically active, free cortisol that is responsible for the signs and symptoms of hypercortisolism. UFC is a sensitive test for the various types of adrenocortical dysfunction, particularly hypercortisolism (Cushing syndrome). A measurement of 24-hour UFC excretion, by liquid chromatography-tandem mass spectrometry (LC-MS/MS), is the preferred screening test for Cushing syndrome. LC-MS/MS methodology eliminates analytical interferences including carbamazepine (Tegretol) and synthetic corticosteroids, which can affect immunoassay-based cortisol results.

**Useful For:** Investigating suspected hypercortisolism when a 24-hour collection is prohibitive (ie, pediatric patients)

**Interpretation:** Most patients with Cushing syndrome have increased 24-hour urinary excretion of cortisol. Further studies, including suppression or stimulation tests, measurement of serum corticotropin (adrenocorticotropic hormone) concentrations, and imaging are usually necessary to confirm the diagnosis and determine the etiology. Values in the normal range may occur in patients with mild Cushing syndrome or with periodic hormonogenesis. In these cases, continuing follow-up and repeat testing are necessary to confirm the diagnosis. Patients with Cushing syndrome due to intake of synthetic glucocorticoids should have suppressed cortisol. In these circumstances a synthetic glucocorticoid screen might be ordered (SGSU / Synthetic Glucocorticoid Screen, Urine). Suppressed cortisol values may also be observed in primary adrenal insufficiency and hypopituitarism. The optimal specimen type for evaluation of primary adrenal insufficiency and hypopituitarism is serum (CORT / Cortisol, Serum).

**Reference Values:**

**Males**

0-2 years: 3.0-120 mcg/g creatinine
3-8 years: 2.2-89 mcg/g creatinine
9-12 years: 1.4-56 mcg/g creatinine
13-17 years: 1.0-42 mcg/g creatinine
> or =18 years: 1.0-119 mcg/g creatinine

**Females**

0-2 years: 3.0-120 mcg/g creatinine
3-8 years: 2.2-89 mcg/g creatinine
9-12 years: 1.4-56 mcg/g creatinine
13-17 years: 1.0-42 mcg/g creatinine
> or =18 years: 0.7-85 mcg/g creatinine

Use the conversion factors below to convert each analyte from mcg/g creatinine to nmol/mol creatinine.

**Conversion factor**

Cortisol: mcg/g creatinine x 413 = nmol/mol creatinine

Cortisol molecular weight=362.5
Creatinine molecular weight=149.59

**Clinical References:**

corticoids), plays a critical role in glucose metabolism and in the body’s response to stress. Both hypercortisolism (Cushing disease) and hypo-cortisolism (Addison disease) can cause disease. Cortisol is also used to treat skin disease, allergic disorders, respiratory system disease, inflammatory disorders, and nephrotic syndrome. Cortisol levels are regulated by adrenocorticotropic hormone (ACTH), which is synthesized by the pituitary in response to corticotropin releasing hormone (CRH). CRH is released in a cyclic fashion by the hypothalamus, resulting in diurnal peaks (6-8 a.m.) and nadirs (11 p.m.) in plasma ACTH and cortisol levels. The majority of cortisol circulates bound to corticosteroid-binding globulin (CBG) and albumin. Normally, less than 5% of circulating cortisol is free (unbound). Only free cortisol can access the enzyme transporters in liver, kidney, and other tissues that mediate metabolic and excretory clearance. Historically, measurements of free cortisol have been achieved from indirect means using a ratio known as the free cortisol index. This measurement takes into account the amount of total cortisol and CBG to give a percentage and ultimately absolute value of free cortisol. These methods do not take into account the possible variations in albumin levels. These calculations also rely on CBG which can be lowered in critically ill patients despite normal adrenal function. Equilibrium dialysis best serves to separate free from bound cortisol without disrupting the bound fraction.

Useful For: Assessment of cortisol status in cases where there is known or a suspected abnormality in cortisol-binding proteins or albumin Assessment of adrenal function in the critically ill or stressed patient, thus preventing unnecessary use of glucocorticoid therapy

Interpretation: Cortisol is converted to cortisone in human kidneys and cortisone is less active toward the mineralcorticoid receptor. The conversion of cortisol to cortisone in the kidney is mediated by 11B-hydroxysteroid dehydrogenase isoform-2. Also, cortisol renal clearance will be reduced when there is a deficiency in the cytochrome P450 3A5 (CYP3A5) enzyme as well as a deficiency in P-glycoprotein. Cortisol binding globulin (CBG) has a low capacity and high affinity for cortisol, whereas albumin has a high capacity and low affinity for binding cortisol. Variations in CBG and serum albumin due to renal or liver disease may have a major impact on free cortisol. Based on the study by Bancos,(1) normal ranges of free cortisol found in patients without adrenal insufficiency were: -Free cortisol at baseline: median 0.400 mcg/dL (interquartile range: IQR 2.5-97.5% - 0.110-1.425 mcg/dL) -Free cortisol at 30 minutes: median 1.355 mcg/dL (IQR 2.5-97.5% - 0.885-2.440 mcg/dL) -Free cortisol at 60 minutes: median 1.720 mcg/dL (IQR 2.5-97.5% - 1.230-2.930 mcg/dL). Based on the study by Bancos,(1) the following cutoffs were calculated for exclusion of adrenal insufficiency: -Free cortisol at baseline*: greater than 0.271 mcg/dL (>271 ng/dL, area under the curve: AUC 0.81) -Free cortisol at 30 minutes: greater than 0.873 mcg/dL (>873 ng/dL, AUC 0.99) -Free cortisol at 60 minutes: greater than 1.190 mcg/dL (>1,190 ng/dL, AUC 0.99) (*Note that baseline free cortisol should not be used to exclude adrenal insufficiency given low performance). The use of free cortisol in the management of glucocorticoid levels in the stressed patient due to major surgery or trauma requires further studies to establish clinical dosing levels and efficacy.

Reference Values:
6-10:30 a.m. Collection: 0.121-1.065 mcg/dL


CIVC 6347

Cortisol, Inferior Vena Cava, Serum

Reference Values:
No established reference values

CIVC 6347

Cortisol, Inferior Vena Cava, Serum

Reference Values:
No established reference values
CLAV 6346  
**Cortisol, Left Adrenal Vein, Serum**  
**Reference Values:**  
No established reference values

CRAV 6345  
**Cortisol, Right Adrenal Vein, Serum**  
**Reference Values:**  
No established reference values

SALCT 84225  
**Cortisol, Saliva**  
**Clinical Information:** Cortisol levels are regulated by adrenocorticotropic hormone (ACTH), which is synthesized by the pituitary in response to corticotropin-releasing hormone (CRH). Cushing syndrome results from overproduction of glucocorticoids as a result of either primary adrenal disease (adenoma, carcinoma, or nodular hyperplasia) or an excess of ACTH (from a pituitary tumor or an ectopic source). ACTH-dependent Cushing syndrome due to a pituitary corticotroph adenoma is the most frequently diagnosed subtype; most commonly seen in women in the third through fifth decades of life. CRH is released in a cyclic fashion by the hypothalamus, resulting in diurnal peaks (elevated in the morning) and nadirs (low in the evening) for plasma ACTH and cortisol levels. The diurnal variation is lost in patients with Cushing syndrome and these patients have elevated levels of evening plasma cortisol. The measurement of late-night salivary cortisol is an effective and convenient screening test for Cushing syndrome.(1) In a recent study from the National Institute of Health, nighttime salivary cortisol measurement was superior to plasma and urine free cortisol assessments in detecting patients with mild Cushing syndrome.(2) The sensitivity of nighttime salivary cortisol measurements remained superior to all other measures. The distinction between Cushing syndrome and pseudo-Cushing states is most difficult in the setting of mild-to-moderate hypercortisolism. Subtle increases in salivary cortisol at the midnight cortisol (cortisol of nadir) appear to be one of the earliest abnormalities in Cushing syndrome.  

**Useful For:** Screening for Cushing syndrome Diagnosis of Cushing syndrome in patients presenting with symptoms or signs suggestive of the disease  

**Interpretation:** Cushing syndrome is characterized by increased salivary cortisol levels, and late-night saliva cortisol measurements may be the optimum test for the diagnosis of Cushing syndrome. It is standard practice to confirm elevated results at least once. This can be done by repeat late-night salivary cortisol measurements, midnight blood sampling for cortisol (CORT / Cortisol, Serum), 24-hour urinary free cortisol collection (CORTU / Cortisol, Free, 24 Hour, Urine), or overnight dexamethasone suppression testing. Upon confirmation of the diagnosis, the cause of hypercortisolism, adrenal versus pituitary versus ectopic adrenocorticotropic hormone production, needs to be established. This is typically a complex undertaking, requiring dynamic testing of the pituitary adrenal axis and imaging procedures. Referral to specialized centers or in-depth consultation with experts is strongly recommended.  

**Reference Values:**  
7 a.m.-9 a.m.: 100-750 ng/dL  
3 p.m.-5 p.m.: <401 ng/dL  
11 p.m.-midnight: <100 ng/dL  


CORT 8545  
**Cortisol, Serum**  
**Current as of October 11, 2018 2:20 pm CDT  
800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com**
Clinical Information: Cortisol, the main glucocorticoid (representing 75%-90% of the plasma corticoids) plays a central role in glucose metabolism and in the body’s response to stress. Cortisol levels are regulated by adrenocorticotropic hormone (ACTH), which is synthesized by the pituitary in response to corticotropin-releasing hormone (CRH). CRH is released in a cyclic fashion by the hypothalamus, resulting in diurnal peaks (6 a.m.-8 a.m.) and nadirs (11 p.m.) in plasma ACTH and cortisol levels. The majority of cortisol circulates bound to cortisol-binding globulin (CBG-transcortin) and albumin. Normally, <5% of circulating cortisol is free (unbound). The “free” cortisol is the physiologically active form. Free cortisol is filterable by the renal glomerulus. Although hypercortisolism is uncommon, the signs and symptoms are common (eg, obesity, high blood pressure, increased blood glucose concentration). The most common cause of increased plasma cortisol levels in women is a high circulating concentration of estrogen (eg, estrogen therapy, pregnancy) resulting in increased concentration of cortisol-binding globulin. Spontaneous Cushing syndrome results from overproduction of glucocorticoids as a result of either primary adrenal disease (adenoma, carcinoma, or nodular hyperplasia) or an excess of ACTH (from a pituitary tumor or an ectopic source). ACTH-dependent Cushing syndrome due to a pituitary corticotroph adenoma is the most frequently diagnosed subtype; most commonly seen in women in the third through the fifth decades of life. The onset is insidious and usually occurs 2 to 5 years before a clinical diagnosis is made. Causes of hypocortisolism are: -Addison disease-primary adrenal insufficiency -Secondary adrenal insufficiency: --Pituitary insufficiency --Hypothalamic insufficiency -Congenital adrenal hyperplasia-defects in enzymes involved in cortisol synthesis

Useful For: Discrimination between primary and secondary adrenal insufficiency Differential diagnosis of Cushing syndrome

Interpretation: In primary adrenal insufficiency, adrenocorticotropic hormone (ACTH) levels are increased and cortisol levels are decreased; in secondary adrenal insufficiency, both ACTH and cortisol levels are decreased. When symptoms of glucocorticoid deficiency are present and the 8 a.m. plasma cortisol value is <10 mcg/dL (or the 24-hour urinary free cortisol value is <50 mcg/24 hours), further studies are needed to establish the diagnosis. First, the basal plasma ACTH concentration should be measured, followed by the short cosyntropin stimulation test. Other frequently used tests are the metyrapone, and insulin-induced hypoglycemia test. Consult the Endocrine Testing Center at 800-533-1710 extension 4-2148 for testing information and interpretation of test results. Cushing syndrome is characterized by increased serum cortisol levels. However, the 24-hour urinary free cortisol excretion is the preferred screening test for Cushing syndrome, specifically CORTU / Cortisol, Free, 24 Hour, Urine that utilizes high-performance liquid chromatography/triple quadrupole-mass spectrometry (LC-MS/MS). A normal result makes the diagnosis unlikely. When cortisol measurement by immunoassay gives results that are not consistent with clinical symptoms, or if patients are known to or suspected of taking exogenous synthetic steroids, consider testing by LC-MS/MS; see CINP / Cortisol, Serum, LC-MS/MS. For confirming the presence of synthetic steroids, order SGSS / Synthetic Glucocorticoid Screen, Serum.

Reference Values:
- a.m.: 7-25 mcg/dL
- p.m.: 2-14 mcg/dL

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.

releasing hormone (CRH). CRH is released in a cyclic fashion by the hypothalamus, resulting in diurnal peaks (6-8 a.m.) and nadirs (11 p.m.) in plasma ACTH and cortisol levels. The majority of cortisol circulates bound to corticosteroid-binding globulin and albumin. Normally, <5% of circulating cortisol is free (unbound). Free cortisol is the physiologically active form, and is filterable by the renal glomerulus. Pathological hypercortisolism due to endogenous or exogenous glucocorticoids is termed Cushing syndrome. Signs and symptoms of pathological hypercortisolism may include central obesity, hypertension, hyperglycemia, hirsutism, muscle weakness, and osteoporosis. However, these symptoms and signs are not specific for pathological hypercortisolism. The majority of individuals with some or all of the symptoms and signs will not suffer from Cushing syndrome. When Cushing syndrome is present, the most common cause is iatrogenic, due to repeated or prolonged administration of, mostly, synthetic corticosteroids. Spontaneous Cushing syndrome is less common and results from either primary adrenal disease (adenoma, carcinoma, or nodular hyperplasia) or an excess of ACTH (from a pituitary tumor or an ectopic source). ACTH-dependent Cushing syndrome due to a pituitary corticotroph adenoma is the most frequently diagnosed subtype; most commonly seen in women in the third through fifth decades of life. The onset is insidious and usually occurs 2 to 5 years before a clinical diagnosis is made. Hypocortisolism most commonly presents with nonspecific lassitude, weakness, hypotension, and weight loss. Depending on the cause, hyperpigmentation may be present. More advanced cases and patients submitted to physical stress (ie, infection, spontaneous or surgical trauma) also may present with abdominal pain, hyponatremia, hyperkalemia, hypoglycemia, and in extreme cases, cardiovascular shock and renal failure. The more common causes of hypocortisolism are: Primary adrenal insufficiency: Addison disease -Congenital adrenal hyperplasia, defects in enzymes involved in cortisol synthesis Secondary adrenal insufficiency: Prior, prolonged corticosteroid therapy -Pituitary insufficiency -Hypothalamic insufficiency See Steroid Pathways in Special Instructions.

Useful For: Second-order testing when cortisol measurement by immunoassay (eg, CORT / Cortisol, Serum) gives results that are not consistent with clinical symptoms, or if patients are known to, or suspected of, taking exogenous synthetic steroids. For confirming the presence of synthetic steroids, order SGSS / Synthetic Glucocorticoid Screen, Serum. An adjunct in the differential diagnosis of primary and secondary adrenal insufficiency An adjunct in the differential diagnosis of Cushing syndrome

Interpretation: In primary adrenal insufficiency, adrenocorticotropic hormone (ACTH) levels are increased and cortisol levels are decreased; in secondary adrenal insufficiency both ACTH and cortisol levels are decreased. When symptoms of glucocorticoid deficiency are present and the 8 a.m. plasma cortisol value is <10 mcg/dL (or the 24-hour urinary free cortisol value is <50 mcg/24 hours), further studies are needed to establish the diagnosis. The 3 most frequently used tests are the ACTH (cosyntropin) stimulation test, the metyrapone test, and insulin-induced hypoglycemia test. First, the basal plasma ACTH concentration should be measured and the short cosyntropin stimulation test performed. Cushing syndrome is characterized by increased serum cortisol levels. However, the 24-hour urinary free cortisol excretion is the preferred screening test for Cushing syndrome, specifically CORTU / Cortisol, Free, 24 Hour, Urine that utilizes liquid chromatography-tandem mass spectrometry. A normal result makes the diagnosis unlikely. Symptoms or signs of Cushing syndrome in a patient with low serum and urine cortisol levels suggest possible exogenous synthetic steroid effects.

Reference Values:
5-25 mcg/dL (a.m.)
2-14 mcg/dL (p.m.)

Pediatric reference ranges are the same as adults, as confirmed by peer-reviewed literature.


Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 649
Cortisol/Cortisone, Free, 24 Hour, Urine

Clinical Information: Cortisol is a steroid hormone synthesized from cholesterol by a multienzyme cascade in the adrenal glands. It is the main glucocorticoid in humans and acts as a gene transcription factor influencing a multitude of cellular responses in virtually all tissues. Cortisol plays a critical role in glucose metabolism, maintenance of vascular tone, immune response regulation, and in the body's response to stress. Its production is under hypothalamic-pituitary feedback control. Only a small percentage of circulating cortisol is biologically active (free), with the majority of cortisol inactive (protein bound). As plasma cortisol values increase, free cortisol (ie, unconjugated cortisol or hydrocortisone) increases and is filtered through the glomerulus. Urinary free cortisol (UFC) correlates well with the concentration of plasma free cortisol. UFC represents excretion of the circulating, biologically active, free cortisol that is responsible for the signs and symptoms of hypercortisolism. UFC is a sensitive test for the various types of adrenocortical dysfunction, particularly hypercortisolism (Cushing syndrome). A measurement of 24-hour UFC excretion, by liquid chromatography-tandem mass spectrometry (LC-MS/MS), is the preferred screening test for Cushing syndrome. LC-MS/MS methodology eliminates analytical interferences including carbamazepine (Tegretol) and synthetic corticosteroids, which can affect immunoassay-based cortisol results. Cortisone, a downstream metabolite of cortisol, provides an additional variable to assist in the diagnosis of various adrenal disorders, including abnormalities of 11-beta-hydroxy steroid dehydrogenase (11-beta HSD), the enzyme that converts cortisol to cortisone. Deficiency of 11-beta HSD results in a state of mineralocorticoid excess because cortisol (but not cortisone) acts as a mineralocorticoid receptor agonist. Licorice (active component glycyrrhetinic acid) inhibits 11-beta HSD and excess consumption can result in similar changes.

Useful For: Screening test for Cushing syndrome (hypercortisolism) Assisting in diagnosing acquired or inherited abnormalities of 11-beta-hydroxy steroid dehydrogenase (cortisol to cortisone ratio) Diagnosis of pseudo-hyperaldosteronism due to excessive licorice consumption This test has limited usefulness in the evaluation of adrenal insufficiency.

Interpretation: Most patients with Cushing syndrome have increased 24-hour urinary excretion of cortisol and/or cortisone. Further studies, including suppression or stimulation tests, measurement of serum corticotropin (adrenocorticotropic hormone) concentrations, and imaging are usually necessary to confirm the diagnosis and determine the etiology. Values in the normal range may occur in patients with mild Cushing syndrome or with periodic hormonogenesis. In these cases, continuing follow-up and repeat testing are necessary to confirm the diagnosis. Patients with Cushing syndrome due to intake of synthetic glucocorticoids should have both suppressed cortisol and cortisone. In these circumstances a synthetic glucocorticoid screen might be ordered (call 800-533-1710). Suppressed cortisol and cortisone values may also be observed in primary adrenal insufficiency and hypopituitarism. However, random urine specimens are not useful for evaluation of hypocorticalism. Further, many normal individuals also may exhibit a very low 24-hour urinary cortisol excretion with considerable overlap with the values observed in pathological hypocorticalism. Therefore, without other tests, 24-hour urinary cortisol measurements cannot be relied upon for the diagnosis of hypocorticalism. Patients with 11-beta HSD deficiency may have cortisone to cortisol ratios <1, whereas a ratio of 2:1 to 3:1 is seen in normal patients. Excessive licorice consumption and use of carbenoxolone, a synthetic derivative of glycyrrhizinic acid used to treat gastroesophageal reflux disease, also may suppress the ratio to <1.

Reference Values:

**CORTISOL**
- 0-2 years: not established
- 3-8 years: 1.4-20 mcg/24 hours
- 9-12 years: 2.6-37 mcg/24 hours
- 13-17 years: 4.0-56 mcg/24 hours
- > or =18 years: 3.5-45 mcg/24 hours

**CORTISONE**
- 0-2 years: not established
3-8 years: 5.5-41 mcg/24 hours  
9-12 years: 9.9-73 mcg/24 hours  
13-17 years: 15-108 mcg/24 hours  
> or =18 years: 17-129 mcg/24 hours

Use the factors below to convert each analyte from mcg/24 hours to nmol/24 hours:

Conversion factors
- Cortisol: mcg/24 hours x 2.76 = nmol/24 hours (molecular weight=362.5)
- Cortisone: mcg/24 hours x 2.78 = nmol/24 hours (molecular weight=360)

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.

**Clinical References:**  

**Cortisol/Cortisone, Free, Random, Urine**

**Clinical Information:** Cortisol is a steroid hormone synthesized from cholesterol by a multienzyme cascade in the adrenal glands. It is the main glucocorticoid in humans and acts as a gene transcription factor influencing a multitude of cellular responses in virtually all tissues. It plays a critical role in glucose metabolism, maintenance of vascular tone, immune response regulation, and in the body's response to stress. Its production is under hypothalamic-pituitary feedback control. Only a small percentage of circulating cortisol is biologically active (free), with the majority of cortisol inactive (protein bound). As plasma cortisol values increase, free cortisol (ie, unconjugated cortisol or hydrocortisone) increases and is filtered through the glomerulus. Urinary free cortisol (UFC) correlates well with the concentration of plasma free cortisol. UFC represents excretion of the circulating, biologically active, free cortisol that is responsible for the signs and symptoms of hypercortisolism. UFC is a sensitive test for the various types of adrenocortical dysfunction, particularly hypercortisolism (Cushing syndrome). A measurement of 24-hour UFC excretion, by liquid chromatography-tandem mass spectrometry (LC-MS/MS), is the preferred screening test for Cushing syndrome. LC-MS/MS methodology eliminates analytical interferences including carbamazepine (Tegretol) and synthetic corticosteroids, which can affect immunoassay-based cortisol results. Cortisone, a downstream metabolite of cortisol, provides an additional variable to assist in the diagnosis of various adrenal disorders, including abnormalities of 11-beta-hydroxy steroid dehydrogenase (11-beta HSD), the enzyme that converts cortisol to cortisone. Deficiency of 11-beta HSD results in a state of mineralocorticoid excess because cortisol (but not cortisone) acts as a mineralocorticoid receptor agonist. Licorice (active component glycyrrhetinic acid) inhibits 11-beta HSD and excess consumption can result in similar changes.

**Useful For:** Investigating suspected Cushing syndrome (hypercortisolism), when a 24-hour collection is prohibitive (ie, pediatric patients). Assisting in diagnosing acquired or inherited abnormalities of 11-beta-hydroxy steroid dehydrogenase (cortisol to cortisone ratio) Diagnosis of pseudo-hyperaldosteronism due to excessive licorice consumption

**Interpretation:** Most patients with Cushing syndrome have increased urinary excretion of cortisol and/or cortisone. Further studies, including suppression or stimulation tests, measurement of serum corticotrophin concentrations, and imaging are usually necessary to confirm the diagnosis and determine the etiology. Values in the normal range may occur in patients with mild Cushing syndrome or with periodic hormonogenesis. In these cases, continuing follow-up and repeat testing are necessary to confirm the diagnosis. Patients with Cushing syndrome due to intake of synthetic glucocorticoids should have both suppressed cortisol and cortisone. In these circumstances a synthetic glucocorticoid screen might be ordered (SGSU / Synthetic Glucocorticoid Screen, Urine). Suppressed cortisol and
cortisone values may also be observed in primary adrenal insufficiency and hypopituitarism. However, random urine specimens are not useful for evaluation of hypocorticalism. Patients with 11-beta HSD deficiency may have cortisone to cortisol ratios less than 1, whereas a ratio of 2 or 3:1 is seen in normal patients. Excessive licorice consumption and use of carbenoxolone, a synthetic derivative of glycyrrhizinic acid used to treat gastroesophageal reflux disease, also may suppress the ratio to less than 1.

Reference Values:
CORTISOL
Males
0-2 years: 3.0-120 mcg/g creatinine
3-8 years: 2.2-89 mcg/g creatinine
9-12 years: 1.4-56 mcg/g creatinine
13-17 years: 1.0-42 mcg/g creatinine
> or =18 years: 1.0-119 mcg/g creatinine
Females
0-2 years: 3.0-120 mcg/g creatinine
3-8 years: 2.2-89 mcg/g creatinine
9-12 years: 1.4-56 mcg/g creatinine
13-17 years: 1.0-42 mcg/g creatinine
> or =18 years: 0.7-85 mcg/g creatinine

CORTISONE
0-2 years: 25-477 mcg/g creatinine
3-8 years: 11-211 mcg/g creatinine
9-12 years: 5.8-109 mcg/g creatinine
13-17 years: 5.4-102 mcg/g creatinine
18-29 years: 5.7-153 mcg/g creatinine
30-39 years: 6.6-176 mcg/g creatinine
40-49 years: 7.6-203 mcg/g creatinine
50-59 years: 8.8-234 mcg/g creatinine
60-69 years: 10-270 mcg/g creatinine
> or =70 years: 12-311 mcg/g creatinine

Use the conversion factors below to convert each analyte from mcg/g creatinine to nmol/mol creatinine:

Conversion factors
Cortisol: mcg/g creatinine x 413=nmol/mol creatinine
Cortisone: mcg/g creatinine x 415=nmol/mol creatinine

Cortisol molecular weight=362.5
Cortisone molecular weight=360.4
Creatinine molecular weight=149.59


Corynebacterium diphtheriae Culture
Clinical Information: Corynebacterium diphtheriae is the etiological agent of diphtheria and occurs in 2 forms, respiratory and cutaneous diphtheria. Respiratory diphtheria may be further classified into pharyngeal, tonsillar, laryngeal, and the less common anterior nasal diphtheria. Due to vaccination programs in the United States, diphtheria is now a rarely reported disease. Corynebacterium diphtheriae is primarily spread by droplets from coughing or sneezing. The incubation period averages 2 to 5 days. The
illness is characterized by fever, malaise, and sore throat with a distinguishing thick pseudomembrane present over the involved mucosa. A swab from beneath the pseudomembrane is the preferred specimen for culture. The organisms multiplying at the infection site produce a toxin, diphtheria toxin, which may result in systemic complications affecting the heart, nervous system, etc. In patients with a clinical diagnosis of possible diphtheria, appropriate specimens should be collected for culture; patients should be placed in appropriate isolation and consideration given to administration of empiric antitoxin (available in the United States through the Centers for Disease Control and prevention) and antibiotics; respiratory and airway support may be required.

Useful For: Confirmation of the clinical diagnosis of diphtheria

Interpretation: A positive result supports a diagnosis of diphtheria. The pathogenesis of the associated disease relates to production phage-encoded diphtheria toxin. Since isolates of Corynebacterium diphtheriae may or may not harbor genes to produce the toxin, they should be further tested for diphtheria toxin production. A negative result is evidence against a diagnosis of diphtheria but does not definitively rule out this disease since culture may be negative because of prior antimicrobial therapy or organism present below the limit of detection of the assay.

Reference Values:
No growth of Corynebacterium diphtheriae


Cotton Fiber, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
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<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69   Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49   Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4   Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9   Strongly positive</td>
</tr>
</tbody>
</table>
CSED 82804

Cottonseed, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>4</td>
<td>17.5-49.9</td>
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</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive               Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


CTWD 82748

Cottonwood, IgE

Clinical Information: Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>Positive</td>
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<td>3</td>
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<td>Strongly positive               Reference values apply to all ages.</td>
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Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Cow Epithelium, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease
and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
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<td>&lt; 0.35</td>
<td>Negative</td>
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<tr>
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<td>0.35-0.69</td>
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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>≥ 100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**COX2 Immunostain, Technical Component Only**

**Clinical Information:** The enzyme cyclooxygenase-2 (COX-2) promotes synthesis of prostaglandin at sites of inflammation. COX-2 has also been linked to carcinogenesis in a number of different neoplastic tissues. The vast majority of colon cancer shows overexpression of COX-2.

**Useful For:** Identifying normal and neoplastic cells expressing cyclooxygenase-2 (COX-2)

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical Information:** Coxiella burnetii, the causative agent of Q fever, is a small obligate intracellular bacterium, which is distributed ubiquitously in the environment. It is acquired through aerosol exposure and generally causes mild respiratory disease. A small number of acute cases advance to a chronic condition, which typically manifests as endocarditis. If left untreated, Q fever endocarditis may be fatal. Serologic and histopathologic examinations are nonspecific and subjective, respectively, limiting usefulness for patient diagnosis. Evaluation of infected tissue, blood, or serum using PCR may be a useful tool for diagnosing some cases of C burnetii infection. Mayo Medical Laboratories has developed a real-time PCR test that permits rapid identification of C burnetii. The assay targets a unique sequence of the shikimate dehydrogenase gene (aroE) present in C burnetii.

**Useful For:** Aiding in the diagnosis of Coxiella burnetii infection (eg, Q fever)

**Interpretation:** A positive test is diagnostic of Coxiella burnetii infection. A negative test does not negate the presence of the organism or recent disease and may occur due to sequence variability underlying the primers and probes, or the presence of C burnetii in quantities less than the limit of detection of the assay.

**Reference Values:**
Not applicable

**Clinical References:**

Coxiella burnetii (Q Fever), Molecular Detection, PCR, Serum

Clinical Information: Coxiella burnetii, the causative agent of Q fever, is a small obligately intracellular bacterium, which is associated with animals. It is acquired through aerosol exposure and generally causes mild respiratory disease. A small number of acute cases advance to a chronic infection, which typically manifests as endocarditis. Left untreated, Q fever endocarditis may be fatal. Serologic and histopathologic studies may be nonspecific and subjective, respectively, limiting usefulness for patient diagnosis. Evaluation of infected tissue, blood, or serum using PCR may be a useful tool for diagnosing some cases of Coxiella burnetii infection. Mayo Medical Laboratories has developed a real-time PCR test that rapidly detects Coxiella burnetii DNA in clinical specimens by targeting a sequence of the shikimate dehydrogenase gene (aroE) unique to Coxiella burnetii.

Useful For: Diagnosing Coxiella burnetii infection (ie, Q fever)

Interpretation: A positive test is diagnostic of Coxiella burnetii infection. A negative result does not negate the presence of the organism or active disease, as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of Coxiella burnetii in quantities less than the limit of detection of the assay.

Reference Values: Not applicable


CPOXZ

CPOX Gene, Full Gene Analysis

Clinical Information: Hereditary coproporphyria (HCP) is an autosomal dominant (AD) acute hepatic porphyria that presents with clinical attacks of neurologic dysfunction, commonly characterized as abdominal pain. However, these acute attacks are variable and can include vomiting, diarrhea, constipation, urinary retention, acute episodes of neuropathic symptoms, psychiatric symptoms, seizures,
respiratory paralysis, tachycardia, and hypertension. Respiratory paralysis can progress to coma and death. HCP is also associated with cutaneous manifestations, including edema, sun-induced erythema, acute painful photodermatitis, and urticaria. In some cases, patients present with isolated photosensitivity. HCP is caused by AD mutations in the CPOX gene. Mutations may have incomplete penetrance. Homozygous mutations in CPOX have been reported in association with a more severe, phenotypically distinct condition called harderoporphyria that is characterized by neonatal hemolytic anemia with mild residual anemia during childhood and adulthood. Affected patients may also present with skin lesions and fecal harderpophyin accumulation may be observed. This condition is inherited in an autosomal recessive pattern and all patients identified to date have been heterozygous or homozygous for the K404E mutation. For HCP, acute attacks may be prevented by avoiding both endogenous and exogenous triggers. These triggers include porphyrogenic drugs, hormonal contraceptives, fasting, alcohol, tobacco, and cannabis. Fecal porphyrins analysis and quantitative urinary porphyrins analysis are helpful in distinguishing HCP from other forms of acute porphyria.

**Useful For:** Confirmation of hereditary coproporphyria (HCP) for patients with clinical features. This test should be ordered only for individuals with symptoms suggestive of HCP. Asymptomatic patients with a family history of HCP should not be tested until a mutation has been identified in an affected family member.

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FCRAB 57674**

**Crab IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**CRAB 82745**

**Crab, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

Class | IgE kU/L | Interpretation
---|---|---
0 | Negative
1 | 0.35-0.69 | Equivocal
2 | 0.70-3.49 | Positive
3 | 3.50-17.4 | Positive
4 | 17.5-49.9 | Strongly positive
5 | 50.0-99.9 | Strongly positive
6 | > or =100 | Strongly positive

Reference values apply to all ages.


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**CRANB 86307 Cranberry, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
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<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
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<td>1</td>
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<td>Equivocal</td>
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<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


---

**Crayfish, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
</tbody>
</table>

**Creatine Disorders Panel, Urine**

Clinical Information: Disorders of creatine synthesis (deficiency of arginine:glycine amidinotransferases: AGAT and guanidinoacetate methyltransferase: GAMT) and creatine transporter (SLC6A8) deficiency are collectively described as creatine deficiency syndromes (CDS). AGAT and GAMT deficiencies are inherited in an autosomal recessive manner, while the creatine transporter defect is X-linked. All 3 disorders result in a depletion of cerebral creatine and typically present with global developmental delays, intellectual disability, and severe speech delay. Commonly, patients with CDS develop seizures. Patients with GAMT and the creatine transporter deficiency exhibit behavioral problems and features of autism. Female carriers for the creatine transporter deficiency can have intellectual disability and behavioral problems, and some develop seizures. Diagnosis is possible by measuring guanidinoacetate (GAA), creatine (Cr), and creatinine (Crn) in plasma and urine. The profiles are specific for each clinical entity. Patients with GAMT deficiency typically exhibit normal to low Cr, very elevated GAA, and low Crn. Patients with AGAT deficiency typically exhibit normal to low Cr, low GAA, and normal to low Crn. In comparison, elevated Cr, normal GAA, normal to low Crn, and an elevated Cr:Crn ratio characterize patients with creatine transporter defect. Treatment with oral supplementation of creatine monohydrate is available and effective for the AGAT and GAMT deficiencies. Early treatment has been reported to prevent disease manifestations in affected but presymptomatic newborn siblings of individuals with GAMT or AGAT deficiencies. Creatine supplementation has not been shown to improve outcomes in males with the creatine transporter defect. Female carriers of creatine transporter deficiency who have symptoms, however, have been reported to benefit from creatine supplementation.

Useful For: Evaluation of patients with a clinical suspicion of inborn errors of creatine metabolism including arginine:glycine amidinotransferase deficiency, guanidinoacetate methyltransferase deficiency, and creatine transporter (SLC6A8) defect

Interpretation: Reports include concentrations of guanidinoacetate, creatine, and creatinine, and a calculated creatine:creatinine ratio. When no significant abnormalities are detected, a simple descriptive interpretation is provided. When abnormal results are detected, a detailed interpretation is given. This interpretation includes an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional biochemical testing.

Reference Values:

<table>
<thead>
<tr>
<th>Age</th>
<th>Creatinine (nmol/mL)</th>
<th>Guanidinoacetate (nmol/mL)</th>
<th>Creatine (nmol/mL)</th>
<th>Creatine/ Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; or ≤31 days</td>
<td>430-5240</td>
<td>9-210</td>
<td>12-2930</td>
<td>0.02-0.93</td>
</tr>
<tr>
<td>32 days-3 months</td>
<td>313-9040</td>
<td>16-860</td>
<td>18-10490</td>
<td>0.02-2.49</td>
</tr>
<tr>
<td>2-4 years</td>
<td>1140-12820</td>
<td>90-1260</td>
<td>200-9210</td>
<td>0.04-1.75</td>
</tr>
<tr>
<td>5-18 years</td>
<td>1190-25270</td>
<td>40-1190</td>
<td>60-9530</td>
<td>0.01-0.96</td>
</tr>
<tr>
<td>&gt;18 years (male)</td>
<td>3854-23340</td>
<td>30-710</td>
<td>7-470</td>
<td>0.00-0.04 Females</td>
</tr>
<tr>
<td>Age</td>
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</table>

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Creatine Kinase (CK), Serum

Clinical Information: Creatine kinase (CK) is an enzyme that catalyzes the reversible phosphorylation of creatine (Cr) by adenosine triphosphate (ATP). Physiologically, when muscle contracts, ATP is converted to adenosine diphosphate (ADP), and CK catalyzes the rephosphorylation of ADP to ATP using creatine phosphate as the phosphorylation reservoir. The CK enzyme is a dimer composed of subunits derived from either muscle (M) or brain (B). Three isoenzymes have been identified: striated muscle (MM), heart tissue (MB), and brain (BB). Normal serum CK is predominantly the CK-MM isoenzyme. CK activity is greatest in striated muscle (MM isoenzyme), heart tissue (MB isoenzyme), and brain (BB isoenzyme). Serum CK concentrations are reflective of muscle mass causing males to have higher concentrations than females. CK may be measured to evaluate myopathy and to monitor patients with rhabdomyolysis for acute kidney injury.

Useful For: Diagnosing and monitoring myopathies or other trauma, toxin, or drug-induced muscle injury

Interpretation: Serum creatine kinase (CK) activity may increase in patients with acute cerebrovascular disease or neurosurgical intervention and with cerebral ischemia as well as in nearly all patients when injury, inflammation, or necrosis of skeletal or heart muscle occurs, including: - All types of muscular dystrophy particularly in progressive muscular dystrophy (particularly Duchenne sex-linked muscular dystrophy). - Viral myositis, polymyositis, and similar muscle diseases - Malignant hyperthermia, an inherited life-threatening condition characterized by high fever and brought on by administration of inhalation anesthesia - Muscle trauma, which causes CK elevations within 12 hours of onset, peaking within 1 to 3 days, and declining 3 to 5 days after cessation of muscle injury --- Serum CK activities exceeding 200 times the upper reference limit may be found in acute rhabdomyolysis, putting the patient at great risk for developing acute renal failure. - When given at pharmacologic doses, some drugs including statins, fibrates, antiretrovirals, and angiotensin II receptor antagonists - Endocrine myopathy, for which hypothyroidism is a common cause, about 60% of hypothyroid subjects show an average elevation of CK activity 5-fold greater than the upper reference limit - Normal childbirth causes a 6-fold elevation in maternal serum For detection of myocardial infarction, changes in serum CK and its heart tissue (MB) isoenzyme have been largely replaced by the more cardiac-specific nonenzymatic markers, cardiac troponin I or T.

Reference Values:

Males
< or =3 months: not established
>3 months: 39-308 U/L

Females
< or =3 months: not established
>3 months: 26-192 U/L

Reference values have not been established for patients that are less than 3 months of age.

Note: Strenuous exercise or intramuscular injections may cause transient elevation of creatine kinase
Creatine Kinase Isoenzyme Reflex, Serum

Clinical Information: Creatine kinase (CK) activity is found in the cytoplasm of several human tissues; major sources of CK include skeletal muscle, myocardium, and the brain. Cytoplasmic CK isoenzymes are dimers of the subunits M and B (MM, MB, or BB). Brain tissue contains predominantly CK-BB (CK1). Skeletal muscle contains almost exclusively CK-MM (CK3). The myocardium contains approximately 30% of CK-MB (CK2), which has been called the "heart-specific" isoenzyme. CK-MB is increased in acute myocardial infarction (AMI); however, CK-MB has been replaced by troponin as the preferred biomarker for the diagnosis of AMI. Mitochondrial CK, located at the outer surface of the inner mitochondrial membrane, has been suggested to catalyze the rate-limiting step of energy transfer from mitochondrial adenosine triphosphate (ATP) with the formation of creatine phosphatase (CP). The CP molecule, which is smaller in size than ATP, diffuses to target organelles in the cytoplasm where its energy is transferred to ATP by cytoplasmic CK. CK activity results in nonaerobic production of ATP in muscle tissues during work. Macro CK refers to at least 2 forms of CK. Macro CK type I is an antibody-bound form of cytoplasmic CK. It migrates between CK-MM and CK-MB. Macro CK type II (mitochondrial CK) migrates slightly cathodic of CK-MM. Detection of macro forms of CK is the primary reason for electrophoresis of CK activity.

 Useful For: Detecting the macro forms of creatine kinase (CK) Identifying the source of a CK elevation

Interpretation: Creatine kinase (CK)-MB appears in serum 4 to 6 hours after the onset of pain in a myocardial infarction, peaks at 18 to 24 hours, and may persist for 72 hours. CK-MB may also be elevated in cases of carbon monoxide poisoning, pulmonary embolism, hypothyroidism, crush injuries, and muscular dystrophy. Extreme elevations of CK-MB can be associated with skeletal muscle cell turnover as in polymyositis, and to a lesser degree in rhabdomyolysis, as seen in strenuous exercise, particularly in the conditioned athlete. CK-BB can be elevated in patients with head injury, in neonates, and in some cancers such as prostate cancer and small cell carcinoma of the lung. It can also be elevated in other malignancies; however, the clinical usefulness of CK-BB as a tumor marker needs further investigation. The presence of macro CK can explain an elevation of total CK. It does not rise and fall as rapidly as CK-MM and CK-MB in muscle injury. Macro CK type II (mitochondrial CK) is rarely observed. It is only seen in acutely ill patients with malignancies and other severe illnesses with a high-associated mortality, such as liver disease and hypoxic injury.

Reference Values:

CREATINE KINASE, TOTAL
Males
< or ≥3 months: not established
>3 months: 39-308 U/L
Females
< or ≥3 months: not established
>3 months: 26-192 U/L
Reference values have not been established for patients that are less than 3 months of age.
Note: Strenuous exercise or intramuscular injections may cause transient elevation of creatine kinase (CK).

CREATINE KINASE ISOENZYMES
MM: 100%
MB: 0%
BB: 0%

Creatinine Clearance, Serum and 24-Hour Urine

Clinical Information: Estimated GFR using serum creatinine alone. Estimated glomerular filtration rate (eGFR) is calculated using the 2009 chronic kidney disease (CKD) Epidemiology Collaboration (CKD-EPI) equation: eGFR(CKD-EPI) =141 x min(Scr/k, 1)alpha x max(Scr/k,1)-1.209 x 0.993age x 0.109 x 1.159 -where age is in years -k is 0.7 for females and 0.9 for males -alpha is -0.329 for females and -0.411 for males -min indicates the minimum of Scr/k or 1 -max indicates the maximum of Scr/k or 1 Use of an estimating or prediction equation to estimate GFR from serum creatinine should be employed for people with CKD and those with risk factors for CKD (diabetes, hypertension, cardiovascular disease, and family history of kidney disease). Reasons given for routine reporting of eGFR with every serum creatinine in adult (18 and over) patients include: -GFR and creatinine clearance are poorly inferred from serum creatinine alone. GFR and creatinine clearance are inversely and nonlinearly related to serum creatinine. The effects of age, sex, and, to a lesser extent, race, on creatinine production further cloud interpretation. -Creatinine is commonly measured in routine clinical practice. Albuminuria (>30 mg/24 hour or urine albumin to creatinine ratio >30mg/g) may be a more sensitive marker of early renal disease, especially among patients with diabetic nephropathy. However, there is poor adherence to guidelines that suggest annual urinary albumin testing of patients with known diabetes. Therefore, if a depressed eGFR is calculated from a serum creatinine measurement, it may help providers recognize early CKD and pursue appropriate follow-up testing and therapeutic intervention. -Monitoring of kidney function (by GFR or creatinine clearance) is essential once albuminuria is discovered. Estimated GFR is a more practical means to closely follow changes in GFR over time, when compared to direct measurement using methods such as iothalamate clearance. -The CKD-EPI equation does not require weight or height variables. From a serum creatinine measurement, it generates a GFR result normalized to a standard body surface area (1.73 m2) using sex, age, and race. Unlike the Cockcroft-Gault equation, height and weight, which are often not available in the laboratory information system, are not required. The CKD-EPI equation does require race (African American or non-African American), which also may not be readily available. For this reason, eGFR values for both African Americans and non-African Americans are reported. The difference between the 2 estimates is typically about 20%. The patient or provider can decide which result is appropriate for a given patient. The Kidney Disease: Improving Global Outcomes (KDIGO) CKD work group clinical practice guidelines,(3) as further defined by the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) commentary,(4) provide the following recommendations for reporting and interpretation of serum creatinine and eGFR: 1.4.3: Evaluation of GFR -1.4.3.1: We recommend using serum creatinine and a GFR estimating equation for initial assessment.(1A) -1.4.3.2: We suggest using additional tests (such as cystatin C or a clearance measurement) for confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate.(2B) 1.4.3.3: We recommend that clinicians (1B): -Use a GFR estimating equation to derive GFR from serum creatinine (eGFRcreat) rather than relying on the serum creatinine concentration alone. Understand clinical settings in which eGFR creat is less accurate. 1.4.3.4: We recommend that clinical laboratories should (1B): -Measure serum creatinine using a specific assay with calibration traceable to the international standard reference materials and minimal bias compared to isotope-dilution mass spectrometry (IDMS) reference methodology. -Report eGFRcreat in addition to the serum creatinine concentration in adults and specify the equation used whenever reporting eGFRcreat. -Report eGFRcreat in adults using the 2009 CKD-EPI creatinine equation. An alternative creatinine-based GFR estimating equation is acceptable if it has been shown to improve accuracy of GFR estimates compared to the 2009 CKD-EPI creatinine equation. When reporting serum creatinine: -We recommend that serum creatinine concentration be reported and rounded to the nearest whole number when expressed as standard international units (mmol/L) and rounded to the nearest 100th of a whole number when expressed as conventional units (mg/dL). When reporting eGFRcreat: -We recommend that eGFRcreat should be reported and rounded to the nearest whole number and relative to
a body surface area of 1.73 m(2) in adults using the units mL/min/1.73 m(2). We recommend eGFRcreat levels less than 60 mL/min/1.73 m(2) should be reported as "decreased". We suggest measuring GFR using an exogenous filtration marker under circumstances where more accurate ascertainment of GFR will impact treatment decisions. Creatinine Clearance Creatinine is derived from the metabolism of creatine from skeletal muscle and dietary meat intake, and is released into the circulation at a relatively constant rate. Thus, the serum creatinine concentration is usually stable. Creatinine is freely filtered by glomeruli and not reabsorbed or metabolized by renal tubules. Therefore, creatinine clearance can be used to assess GFR. However, approximately 15% of excreted urine creatinine is derived from proximal tubular secretion. Because of the tubular secretion of creatinine, creatinine clearance typically overestimates true GFR by 10% to 15%. Creatinine clearance is usually determined from measurement of creatinine in a 24-hour urine specimen and from a serum specimen obtained during the same collection period. However, shorter time periods can be used. A key consideration is accurate timing and collection of the urine sample. Creatinine clearance normalized to body surface area is calculated by the equation:

Patient surface area (SA) = wt (kg) X ht (cm) X 0.007184

Urine conc (mg/dL) X 24 hr urine volume (mL) / 1440 minutes x Plasma creat (mg/dL)

Uncorr creat clear =

Corr creat clear =

Useful For: Estimation of glomerular filtration rate

Interpretation: Decreased creatinine clearance indicates decreased glomerular filtration rate (GFR). This can be due to conditions such as progressive renal disease, or result from adverse effect on renal hemodynamics that are often reversible, including drug effects or decreases in effective renal perfusion (eg, volume depletion, heart failure). Increased creatinine clearance is often referred to as hyperfiltration and is most commonly seen during pregnancy or in patients with early diabetes mellitus, before diabetic nephropathy has occurred. It may also occur with large dietary protein intake. A major limitation of creatinine clearance is that its accuracy worsens in relation to the amount of tubular creatinine secretion. Often as GFR declines, the contribution of urine creatinine from tubular secretion increases, further increasing the discrepancy between true GFR and measured creatinine clearance. Estimated GFR: According to the Kidney Disease: Improving Global Outcomes (KDIGO) CKD work group, chronic kidney disease (CKD) is defined as the abnormalities of kidney structure of function, present for more than 3 months, with implications for health. CKD should be classified by cause, GFR category, and albuminuria category. KDIGO guidelines provide the following GFR categories: Stage Terms GFR mL/min/1.73 m(2) G1* Normal or high 90 G2* Mildly decreased 60 to 89 G3a Mildly to moderately decreased 45 to 59 G3b Moderately to severely decreased 30-44 G4 Severely decreased 15-29 G5 Kidney failure <15 *In the absence of evidence of kidney damage, neither G1 nor G2 fulfill criteria for CKD. Urinary albumin excretion can also be used to further subdivide CKD stages

Reference Values:
Creatinine Clearance
Males:
0-18 years: Reference values have not been established
19-75 years: 77-160 mL/min/BSA
> or =76 years: Reference values have not been established
Females:
0-17 years: Reference values have not been established
18-29 years: 78-161 mL/min/BSA
30-39 years: 72-154 mL/min/BSA
40-49 years: 67-146 mL/min/BSA
50-59 years: 62-139 mL/min/BSA
60-72 years: 56-131 mL/min/BSA
> or =73 years: Reference values have not been established

Creatinine, Urine: reported in units of mg/dL

Creatinine, Serum
Males:

0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-14 years: 0.35-0.86 mg/dL
> or =15 years: 0.74-1.35 mg/dL
Females:
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-15 years: 0.35-0.86 mg/dL
> or =16 years: 0.59-1.04 mg/dL

**Clinical References:**
1. Post TW, Rose BD: Assessment of renal function: plasma creatinine; BUN; and GFR. In Up To Date 9.1. Edited by BD Rose. 2001

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**Creatinine with Estimated GFR (CKD-EPI), Serum**

**Clinical Information:** Creatinine: In muscle metabolism, creatinine is synthesized endogenously from creatine and creatine phosphate. Creatinine is removed from plasma by glomerular filtration into the urine without being reabsorbed by the tubules to any significant extent. Renal tubular secretion also contributes a small quantity of creatinine to the urine. As a result, creatinine clearance often overestimates the true glomerular filtration rate (GFR) by 10% to more than 20%. Determinations of creatinine and renal clearance of creatinine are of value in the assessment of kidney function. Serum or blood creatinine levels in renal disease generally do not increase until renal function is substantially impaired. Estimated glomerular filtration rate (eGFR): eGFR is calculated using the 2009 chronic kidney disease (CKD) epidemiology collaboration (CKD-EPI) equation: 
\[
\text{eGFR (CKD-EPI)} = 141 \times \min(\frac{\text{Scr}}{\text{k}}, 1) \times \alpha \times \max(\frac{\text{Scr}}{\text{k}}, 1)^{-1.209} \times 0.993 \times \text{age}^{0.189} \times 1.018 \times \left(\frac{0.7}{\text{age}^{0.204}}\right) \times 1.159
\]
where age is in years, k is 0.7 for females and 0.9 for males, alpha is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/k or 1, and max indicates the maximum of Scr/k or 1. Use of an estimating or prediction equation to estimate GFR from serum creatinine should be employed for people with CKD and those with risk factors for CKD (diabetes, hypertension, cardiovascular disease, and family history of kidney disease). Reasons given for routine reporting of eGFR with every serum creatinine in adult (18 and over) patients include: - GFR and creatinine clearance are poorly inferred from serum creatinine alone. GFR and creatinine clearance are inversely and nonlinearly related to serum creatinine. The effects of age, sex, and, to a lesser extent, race, on creatinine production further cloud interpretation. - Creatinine is commonly measured in routine clinical practice. Albuminuria (>30 mg/24 hour or urine albumin to creatinine ratio > 30mg/g) may be a more sensitive marker of early renal disease, especially among patients with diabetic nephropathy. However, there is poor adherence to guidelines that suggest annual urinary albumin testing of patients with known diabetes. Therefore, if a depressed eGFR is calculated from a serum creatinine measurement, it may help providers recognize early CKD and pursue appropriate follow-up testing and therapeutic intervention. - Monitoring of kidney function (by GFR or creatinine clearance) is essential once albuminuria is discovered. Estimated GFR is a more practical means to closely follow changes in GFR over time, when compared to direct measurement using methods such as iothalamate clearance. - The CKD-EPI equation does not require weight or height variables. From a serum creatinine measurement, it generates a GFR result normalized to a standard body surface area (1.73 m²) using sex, age, and race. Unlike the Cockcroft-Gault equation, height and weight, which are often not available in the laboratory information system, are not required. The CKD-EPI equation does require race (African American or non-African American), which also may not be readily available. For this reason, eGFR values for both African Americans and non-African Americans are reported. The difference between the 2 estimates is typically about 20%. The patient or provider can decide which result is appropriate for a given patient. The Kidney Disease:
Improving Global Outcomes (KDIGO) CKD work group clinical practice guideline,(3) as further defined by the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) commentary,(4) provide the following recommendations for reporting and interpretation of serum creatinine and eGFR: 1.4.3: Evaluation of GFR -1.4.3.1: We recommend using serum creatinine and a GFR estimating equation for initial assessment. (1A) 1.4.3.2: We suggest using additional tests (such as cystatin C or a clearance measurement) for confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate. (2B) 1.4.3.3: We recommend that clinicians (1B): -Use a GFR estimating equation to derive GFR from serum creatinine (eGFRcreat) rather than relying on the serum creatinine concentration alone. -Understand clinical settings in which eGFRcreat is less accurate. 1.4.3.4: We recommend that clinical laboratories should (1B): -Measure serum creatinine using a specific assay with calibration traceable to the international standard reference materials and minimal bias compared to isotope-dilution mass spectrometry (IDMS) reference methodology. -Report eGFRcreat in addition to the serum creatinine concentration in adults and specify the equation used whenever reporting eGFRcreat. -Report eGFRcreat in adults using the 2009 CKD-EPI creatinine equation. An alternative creatinine-based GFR estimating equation is acceptable if it has been shown to improve accuracy of GFR estimates compared to the 2009 CKD-EPI creatinine equation.

When reporting serum creatinine: -We recommend that serum creatinine concentration be reported and rounded to the nearest whole number when expressed as standard international units (mmol/l) and rounded to the nearest 100th of a whole number when expressed as conventional units (mg/dl). When reporting eGFRcreat: -We recommend that eGFRcreat should be reported and rounded to the nearest whole number and relative to a body surface area of 1.73 m2 in adults using the units ml/min/1.73 m2. -We recommend eGFRcreat levels less than 60 ml/min/1.73 m2 should be reported as "decreased".

1.4.3.8: We suggest measuring GFR using an exogenous filtration marker under circumstances where more accurate ascertainment of GFR will impact treatment decisions (2B)

Useful For: Creatinine: -Diagnosing and monitoring treatment of acute and chronic renal diseases -Adjusting dosage of renally excreted medications -Monitoring renal transplant recipients Estimated Glomerular Filtration Rate (eGFR): Serum creatinine measurement is used in estimating GFR for people with chronic kidney disease (CKD) and those with risk factors for CKD (diabetes, hypertension, cardiovascular disease, and family history of kidney disease)

Interpretation: Creatinine: Because serum creatinine is inversely correlated with glomerular filtration rate (GFR), when renal function is near normal, absolute changes in serum creatinine reflect larger changes than do similar absolute changes when renal function is poor. For example, an increase in serum creatinine from 1 to 2 mg/dL may indicate a decrease in GFR of 50 mL/min (from 100 to 50 mL/min), whereas an increase in serum creatinine level from 4 to 5 mg/dL may indicate a decrease of only 5 mL/min (from 25 to 20 mL/min). Because of the imprecision of serum creatinine as an assessment of GFR, there may be clinical situations where a more accurate GFR assessment must be performed, iothalamate or inulin clearance are superior to serum creatinine and eGFR. Several factors may influence serum creatinine independent of changes in GFR. For instance, creatinine generation is dependent upon muscle mass. Thus, young, muscular males may have significantly higher serum creatinine levels than elderly females, despite having similar GFRs. Also, because some renal clearance of creatinine is due to tubular secretion, drugs that inhibit this secretory component (eg, cimetidine and trimethoprim) may cause small increases in serum creatinine without an actual decrease in GFR. Estimated GFR: According to the Kidney Disease: Improving Global Outcomes (KDIGO) CKD work group, chronic kidney disease (CKD) is defined as the abnormalities of kidney structure or function, present for more than 3 months, with implications for health.(3,4) CKD should be classified by cause, GFR category, and albuminuria category.(3,4) KDIGO guidelines provide the following GFR categories(3,4): Stage Terms GFR mL/min/1.73 m(2) G1* Normal or high 90 G2* Mildly decreased 60 to 89 G3a Mildly to moderately decreased 45 to 59 G3b Moderately to severely decreased 30-44 G4 Severely decreased 15-29 G5 Kidney failure <15 *In the absence of evidence of kidney damage, neither G1 nor G2 fulfill criteria for CKD.

Reference Values:
CREATININE
Males(1)
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-14 years: 0.35-0.86 mg/dL
Creatinine, 24 Hour, Urine

Clinical Information: Creatinine is formed from the metabolism of creatine and phosphocreatine, both of which are principally found in muscle. Thus the amount of creatinine produced is in large part dependent upon the individual's muscle mass and tends not to fluctuate much from day-to-day. Creatinine is not protein-bound and is freely filtered by glomeruli. All of the filtered creatinine is excreted in the urine. Renal tubular secretion of creatinine also contributes to a small proportion of excreted creatinine. Although most excreted creatinine is derived from an individual's muscle, dietary protein intake, particularly of cooked meat, can contribute to urinary creatinine levels. The renal clearance of creatinine provides an estimate of glomerular filtration rate.

Useful For: Urinary creatinine, in conjunction with serum creatinine, is used to calculate the creatinine clearance, a measure of renal function.

Interpretation: 24-Hour urinary creatinine determinations are principally used for the calculation of creatinine clearance. Decreased creatinine clearance indicates decreased glomerular filtration rate. This can be due to conditions such as progressive renal disease, or result from adverse effect on renal hemodynamics that are often reversible including certain drugs or from decreases in effective renal perfusion (eg, volume depletion or heart failure). Increased creatinine clearance is often referred to as "hyperfiltration" and is most commonly seen during pregnancy or in patients with diabetes mellitus, before diabetic nephropathy has occurred. It also may occur with large dietary protein intake.

Reference Values:
Normal values mg per 24 hours:
Males: 955-2936 mg/24 hours
Females: 601-1689 mg/24 hours

Reference ranges for male and female patients <18 and >83 years of age have not been established.

The expected urine creatinine excretion per 24 hours:
Males: 13-29 mg/kg of body weight/24 hours
Females: 9-26 mg/kg of body weight/24 hours

Reference ranges for male and female patients <18 and >83 years of age have not been established.
Note: To convert to mg/kg of body weight/24 hours, divide the mg/24 h result by body weight in kg.

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.

**Clinical References:**

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**Creatinine, Body Fluid**

**Clinical Information:** By-products of nitrogen metabolism are elevated in high concentration in urine compared to blood, and serve as a surrogate marker for the identification of urine leakage into a body compartment. This may occur due to trauma, abdominal or pelvic surgery, and bladder perforation. Concentrations of creatinine or urea nitrogen that exceed the concentration found in a concurrent sample of blood are suggestive of the presence of urine.

**Useful For:** Identifying the presence of urine as a cause for accumulation of fluid in a body compartment

**Interpretation:** Body fluid to serum ratios greater than 1.0 suggests the presence of urine in the sample.

**Reference Values:**
Not applicable

**Clinical References:**

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**Creatinine, Random, Urine**

**Clinical Information:** Creatinine is formed from the metabolism of creatine and phosphocreatine, both of which are principally found in muscle. Thus the amount of creatinine produced is in large part dependent upon the individual’s muscle mass and tends not to fluctuate much from day-to-day. Creatinine is not protein-bound and is freely filtered by glomeruli. All of the filtered creatinine is excreted in the urine. Renal tubular secretion of creatinine also contributes to a small proportion of excreted creatinine. Although most excreted creatinine is derived from an individual’s muscle, dietary protein intake, particularly of cooked meat, can contribute to urinary creatinine levels. The renal clearance of creatinine provides an estimate of glomerular filtration rate (GFR). Since creatinine for the most part in the urine only comes from filtration, the concentration of creatinine reflects overall urinary concentration. Therefore, creatinine can be used to normalize other analytes in a random urine specimen.

**Useful For:** Urinary creatinine, in conjunction with serum creatinine, is used to calculate the creatinine clearance, a measure of renal function. In a random specimen, urinary analytes can be normalized by the creatinine concentration to account for the variation in urinary concentrations between subjects.

**Interpretation:** Decreased creatinine clearance indicates decreased glomerular filtration rate. This can be due to conditions such as progressive renal disease, or result from adverse effect on renal hemodynamics that are often reversible including certain drugs or from decreases in effective renal perfusion (eg, volume depletion or heart failure). Increased creatinine clearance is often referred to as "hyperfiltration" and is most commonly seen during pregnancy or in patients with diabetes mellitus,
before diabetic nephropathy has occurred. It also may occur with large dietary protein intake.

**Reference Values:**
No established reference values

**Clinical References:**

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**Cryoglobulin and Cryofibrinogen Panel, Serum and Plasma**

**Clinical Information:** Cryoglobulins are immunoglobulins that precipitate when cooled and dissolve when heated. Because these proteins precipitate when cooled, patients may experience symptoms when exposed to the cold. Cryoglobulins may be associated with a variety of diseases including plasma cell disorders, autoimmune diseases, and infections. Cryoglobulins may also cause erroneous results with some automated hematology instruments. Cryoglobulins are classified as:
- Type I (monoclonal)
- Type II (mixed--2 or more immunoglobulins of which 1 is monoclonal)
- Type III (polyclonal--in which no monoclonal protein is found)

Type I cryoglobulinemia is associated with monoclonal gammopathy of undetermined significance, macroglobulinemia, or multiple myeloma. Type II cryoglobulinemia is associated with autoimmune disorders such as vasculitis, glomerulonephritis, systemic lupus erythematosus, rheumatoid arthritis, and Sjogren's syndrome. It may be seen in infections such as hepatitis, infectious mononucleosis, cytomegalovirus, and toxoplasmosis. Type II cryoglobulinemia may also be essential, i.e., occurring in the absence of underlying disease. Type III cryoglobulinemia usually demonstrates trace levels of cryoprecipitate, may take up to 7 days to appear, and is associated with the same disease spectrum as Type II cryoglobulinemia. A cryoprecipitate that is seen in plasma but not in serum is caused by cryofibrinogen. Cryofibrinogens are extremely rare and can be associated with vasculitis. Due to the rarity of clinically significant cryofibrinogenemia, testing for cryoglobulins is usually sufficient for investigation of cryoproteins.

**Useful For:**
- Evaluating patients with vasculitis, glomerulonephritis, and lymphoproliferative diseases
- Evaluating patients with macroglobulinemia or myeloma in whom symptoms occur with cold exposure

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
- **CRYOglobulin**
  - Negative (positives reported as percent)
  - If positive after 1 or 7 days, immunotyping of the cryoprecipitate is performed at an additional charge.

- **CRYOFIBRINogen**
  - Negative
  - Quantitation and immunotyping will not be performed on positive cryofibrinogen.


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**Cryoglobulin, Serum**

**Clinical Information:** Cryoglobulins are immunoglobulins that precipitate when cooled and dissolve when heated. Because these proteins precipitate when cooled, patients may experience symptoms when exposed to the cold. Cryoglobulins may be associated with a variety of diseases including plasma cell disorders, autoimmune diseases, and infections. Cryoglobulins may also cause
erroneous results with some automated hematology instruments. Cryoglobulins are classified as:
- Type I (monoclonal)
- Type II (mixed--2 or more immunoglobulins of which 1 is monoclonal)
- Type III (polyclonal--in which no monoclonal protein is found)

Type I cryoglobulinemia is associated with monoclonal gammopathy of undetermined significance, macroglobulinemia, or multiple myeloma. Type II cryoglobulinemia is associated with autoimmune disorders such as vasculitis, glomerulonephritis, systemic lupus erythematosus, rheumatoid arthritis, and Sjogren's syndrome. It may be seen in infections such as hepatitis, infectious mononucleosis, cytomegalovirus, and toxoplasmosis. Type II cryoglobulinemia may also be essential, ie, occurring in the absence of underlying disease. Type III cryoglobulinemia usually demonstrates trace levels of cryoprecipitate, may take up to 7 days to appear, and is associated with the same disease spectrum as Type II cryoglobulinemia.

**Useful For:** Evaluating patients with vasculitis, glomerulonephritis, and lymphoproliferative diseases
Evaluating patients with macroglobulinemia or myeloma in whom symptoms occur with cold exposure

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Negative (positives reported as percent)


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**Cryptococcus Antigen Screen with Titer, Serum**

**Clinical Information:** Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or C gattii. C neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. C gatti was previously only associated with tropical and subtropical regions; however, more recently this organism has also been found to be endemic in British Columbia and among the Pacific Northwest United States, and is associated with several different trees species. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoformans infections occur in immunocompromised patient populations, C gattii is has a higher predilection for infection of healthy hosts.(1,2) In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

**Useful For:** An aid in the diagnosis of cryptococcosis

**Interpretation:** The presence of cryptococcal antigen in any body fluid (serum or cerebrospinal fluid) is indicative of cryptococcosis. Specimens that are positive by the lateral flow assay screen are automatically repeated with the same method utilizing dilutions in order to generate a titer value. Disseminated infection is usually accompanied by a positive serum test. Higher Cryptococcus antigen titers appear to correlate with more severe infections. Declining titers may indicate regression of infection. However, monitoring titers to cryptococcal antigen should not be used as a test of cure or to guide treatment decisions, as low level titers may persist for extended periods of time following appropriate therapy and the resolution of infection.(3)

**Reference Values:**
Negative

Cryptococcus Antigen Screen with Titer, Spinal Fluid

Clinical Information: Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or C. gattii. C. neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. C. gattii was previously only associated with tropical and subtropical regions, however, more recently this organism has also been found to be endemic in British Columbia and among the Pacific Northwest United States, and is associated with several different trees species. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C. neoformans infections occur in immunocompromised patient populations, C. gattii has a higher predilection for infection of healthy hosts.(1,2) In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals. Note: According to the College of American Pathologists (CAP, IMM.41840), cerebrospinal fluid (CSF) samples submitted for initial diagnosis, which test positive by the lateral flow assay, should also be submitted for routine fungal culture. Fungal cultures are not required for CSF samples that are submitted to monitor Cryptococcus antigen titers during treatment.

Useful For: Aids in the diagnosis of cryptococcosis

Interpretation: The presence of cryptococcal antigen in any body fluid (serum or cerebrospinal fluid: CSF) is indicative of cryptococcosis. Specimens that are positive by the lateral flow assay (LFA) screen are automatically repeated by the same method utilizing dilutions in order to generate a titer value. CSF specimens submitted for initial diagnosis, which test positive by LFA, should also be submitted for routine fungal culture. Culture can aid to differentiate between the 2 common Cryptococcus species causing disease (C. neoformans and C. gattii) and can be used for antifungal susceptibility testing, if necessary. CSF specimens submitted to monitor antigen levels during treatment do not need to be cultured. Disseminated infection is usually accompanied by a positive serum test. Higher Cryptococcus antigen titers appear to correlate with more severe infections. Declining titers may indicate regression of infection. However, monitoring titers to cryptococcal antigen should not be used as a test of cure or to guide treatment decisions, as low level titers may persist for extended periods of time following appropriate therapy and the resolution of infection.(3)

Reference Values:
- Negative
- Reference values apply to all ages.

Clinical References:
Cryptococcus Antigen Screen, Lateral Flow Assay, Pleural Fluid

**Clinical Information:** Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or C gattii. C neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. C gattii was previously only associated with tropical and subtropical regions; however, more recently this organism has also been found to be endemic in British Columbia, along the Pacific Northwest, and in the Southeastern United States. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoformans infections occur in immunocompromised patient populations, C gattii has a higher predilection for infection of healthy hosts. In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

**Useful For:** Diagnosis of infection with Cryptococcus species

**Interpretation:** The presence of cryptococcal antigen in pleural fluid is indicative of infection with Cryptococcus species. Monitoring cryptococcal antigen levels as a means to determine response to therapy is discouraged, as antigen levels may persist despite adequate treatment and disease resolution. A negative result indicates lack of infection; however, rare cases of false-negative results have been reported. Fungal culture should always be ordered alongside antigen testing.

**Reference Values:**
Negative


Cryptococcus Antigen Titer, Lateral Flow Assay, Pleural Fluid

**Clinical Information:** Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or C gattii. C neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. C gattii was previously only associated with tropical and subtropical regions; however, more recently this organism has also been found to be endemic in British Columbia, along the Pacific Northwest and in the Southeastern United States. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoformans infections occur in immunocompromised patient populations, C gattii has a higher predilection for infection of healthy hosts. In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

**Useful For:** Diagnosis of infection with Cryptococcus species

**Interpretation:** The presence of cryptococcal antigen in pleural fluid is indicative of infection with Cryptococcus species. Monitoring cryptococcal antigen levels as a means to determine response to
therapy is discouraged, as antigen levels may persist despite adequate treatment and disease resolution. A negative result indicates lack of infection; however rare cases of false-negative results have been reported. Fungal culture should always be ordered alongside antigen testing.

**Reference Values:**
Only orderable as a reflex. For more information see PLFA / Cryptococcus Antigen Screen, Lateral Flow Assay, Pleural Fluid.

**Cryptococcus Antigen Titer, LFA, Serum**

**Clinical Information:** Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoforms or C gattii. C neoforms has been isolated from several sites in nature, particularly weathered pigeon droppings. C gattii was previously only associated with tropical and subtropical regions, however, more recently this organism has also been found to be endemic in British Columbia and among the Pacific Northwest United States, and is associated with several different trees species. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoforms infections occur in immunocompromised patient populations, C gattii has a higher predilection for infection of healthy hosts.(1,2) In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

**Useful For:** Monitoring Cryptococcus antigen titers in serum Aiding in the diagnosis of cryptococcosis

**Interpretation:** The presence of cryptococcal antigen in any body fluid (serum or cerebrospinal fluid: CSF) is indicative of cryptococcosis. Disseminated infection is usually accompanied by a positive serum test. Declining titers may indicate regression of infection. However, monitoring titers to cryptococcal antigen should not be used as a test of cure or to guide treatment decisions. Low-level titers may persist for extended periods of time following appropriate therapy and resolution of infection.(3,4)

**Reference Values:**
Negative

**Clinical References:**
weathered pigeon droppings. C gatti was previously only associated with tropical and subtropical regions, however, more recently this organism has also been found to be endemic in British Columbia and among the Pacific Northwest United States, and is associated with several different trees species. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoformans infections occur in immunocompromised patient populations, C gatti is has a higher predilection for infection of healthy hosts.(1,2) In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals. Note: According to the College of American Pathologists (CAP, IMM.41840), cerebrospinal fluid (CSF) samples submitted for initial diagnosis that test positive by the lateral flow assay should also be submitted for routine fungal culture. Fungal cultures are not required for CSF samples that are submitted to monitor Cryptococcus antigen titers during treatment.

**Useful For:** Monitoring Cryptococcus antigen titers in cerebrospinal fluid

**Aiding in the diagnosis of cryptococcosis**

**Interpretation:** The presence of cryptococcal antigen in any body fluid (serum or cerebrospinal fluid: CSF) is indicative of cryptococcosis. Disseminated infection is usually accompanied by a positive serum test. Declining titers may indicate regression of infection. However, monitoring titers to cryptococcal antigen should not be used as a test of cure or to guide treatment decisions. Low-level titers may persist for extended periods of time following appropriate therapy and resolution of infection.(3,4) CSF specimens submitted for initial diagnosis that test positive by the lateral flow assay, should also be submitted for routine fungal culture. Culture can aid to differentiate between the 2 common Cryptococcus species causing disease (C neoformans and C gattii) and can be used for antifungal susceptibility testing, if necessary. CSF specimens submitted to monitor antigen levels during treatment do not need to be cultured.

**Reference Values:**

Negative


**Cryptococcus Antigen with Reflex, LFA, Spinal Fluid**

**Clinical Information:** Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans or C gattii. C neoformans has been isolated from several sites in nature, particularly weathered pigeon droppings. C gatti was previously only associated with tropical and subtropical regions, however, more recently this organism has also been found to be endemic in British Columbia and among the Pacific Northwest United States, and is associated with several different trees species. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. While the majority of C neoformans infections occur in immunocompromised patient populations, C gattii has a higher predilection for infection of healthy
hosts.(1,2) In addition to the lungs, cryptococcal infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality among patients with CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

Note: According to the College of American Pathologists (CAP, IMM.41840), cerebrospinal fluid (CSF) samples submitted for initial diagnosis, which test positive by the lateral flow assay, should also be submitted for routine fungal culture. Fungal cultures are not required for CSF samples that are submitted to monitor Cryptococcus antigen titers during treatment.

**Useful For:** Aids in the diagnosis of cryptococcosis

**Interpretation:** The presence of cryptococcal antigen in any body fluid (serum or cerebrospinal fluid: CSF) is indicative of cryptococcosis. Specimens that are positive by the lateral flow assay (LFA) screen are automatically repeated by the same method utilizing dilutions in order to generate a titer value. CSF specimens submitted for initial diagnosis, which test positive by LFA, should also be submitted for routine fungal culture. Culture can aid to differentiate between the 2 common Cryptococcus species causing disease (C neoformans and C gattii) and can be used for antifungal susceptibility testing, if necessary. CSF specimens submitted to monitor antigen levels during treatment do not need to be cultured. Disseminated infection is usually accompanied by a positive serum test. Higher Cryptococcus antigen titers appear to correlate with more severe infections. Declining titers may indicate regression of infection. However, monitoring titers to cryptococcal antigen should not be used as a test of cure or to guide treatment decisions, as low level titers may persist for extended periods of time following appropriate therapy and the resolution of infection.

**Reference Values:**

**CRYPTOCOCCUS ANTIGEN SCREEN WITH TITER**
- Negative
  - Reference values apply to all ages.

**CRYPTOCOCCUS ANTIGEN TITER, LFA**
- Negative
  - Reference values apply to all ages.

**FUNGAL CULTURE**
- Negative
  - If positive, fungus will be identified.
  - Reference values apply to all ages.

**Clinical References:**

**Cryptococcus Antigen, Urine**

**Clinical Information:** Cryptococcosis is an invasive fungal infection caused by Cryptococcus neoformans. The organism has been isolated from several sites in nature, particularly weathered pigeon droppings. Infection is usually acquired via the pulmonary route. Patients are often unaware of any exposure history. Approximately half of the patients with symptomatic disease have a predisposing immunosuppressive condition such as AIDS, steroid therapy, lymphoma, or sarcoidosis. Symptoms may include fever, headache, dizziness, ataxia, somnolence, and cough. In addition to the lungs, cryptococcal
infections frequently involve the central nervous system (CNS), particularly in patients infected with HIV. Mortality in CNS cryptococcosis may approach 25% despite antibiotic therapy. Untreated CNS cryptococcosis is invariably fatal. Disseminated disease may affect any organ system and usually occurs in immunosuppressed individuals.

**Useful For:** Aiding in the diagnosis of cryptococcosis

**Interpretation:** The presence of cryptococcal antigen in any body fluid is indicative of cryptococcosis. Higher titers appear to correlate with more severe infections. Declining titers in urine or serum may indicate regression of infection or response to therapy. However, monitoring titers to cryptococcal antigen should not be used as a test of cure, as low level titers may persist for extended periods of time following appropriate therapy and the resolution of infection. In addition to testing for cryptococcal antigen, patients with presumed disease due to Cryptococcus neoformans should have clinical specimens (eg, bronchoalveolar lavage fluid) submitted for routine smear and fungal culture.

**Reference Values:**

Negative


**CRYPS 80335**

**Cryptosporidium Antigen, Feces**

**Clinical Information:** Cryptosporidia are small protozoan parasites conventionally categorized in the coccidian group. They commonly infect humans and animals, including livestock, and can contaminate and survive in recreational and drinking water supplies. Infection of humans occurs by the fecal-oral route or by ingestion of contaminated water. Cryptosporidiosis occurs as a profuse diarrhea that can be prolonged and life-threatening in immunocompromised patients such as those with AIDS. It generally causes a self-limited, moderate diarrhea in immunocompetent individuals. See Parasitic Investigation of Stool Specimens Algorithm and Laboratory Testing for Infectious Causes of Diarrhea in Special Instructions for other diagnostic tests that may be of value in evaluating patients with diarrhea.

**Useful For:** Establishing the diagnosis of intestinal cryptosporidiosis

**Interpretation:** A positive enzyme-linked immunosorbent assay (ELISA) indicates the presence of antigens of cryptosporidium and is interpreted as evidence of infection with that organism. The sensitivity, specificity, and positive predictive value of the ELISA were 87%, 99%, and 98%, respectively, as determined by examination of 231 fecal specimens by conventional microscopy and by ELISA.

**Reference Values:**

Negative

**Clinical References:** Centers for Disease Control and Prevention: Parasites-Cryptosporidium (also known as “Crypto”). Accessed 1/12/2017. Available at www.cdc.gov/parasites/crypto/index.html

**SFC 8719**

**Crystal Identification, Synovial Fluid**

**Clinical Information:** Birefringent crystals are found in the synovial fluid of more than 90% of patients with acutely inflamed joints. Monosodium urate crystals are seen in gouty fluids and calcium pyrophosphate crystals are seen in chondrocalcinosis. The urates are usually needle-shaped, and the calcium crystals are often rhomboidal. Cholesterol crystals may also be observed.

**Useful For:** Identifying the presence and type of crystals in synovial fluid

**Interpretation:** Positive identification of crystals provides a definitive diagnosis for joint disease.

**Reference Values:**
None seen
If present, crystals are identified.

**Clinical References:** Kjeldsberg C, Knight J: Body fluids: Laboratory examination of cerebrospinal, seminal, serous and synovial fluids. Third edition. Chicago, ASCP, 1993, pp 272-283, 292-293

**CSF3R**

**CSF3R Exon 14 and 17 Mutation Detection by Sanger Sequencing, Varies**

**Clinical Information:** CSF3R encodes the receptor for colony-stimulating factor 3, a cytokine that controls the production, differentiation, and function of granulocytes. Somatic CSF3R mutations were recently described in 50% to 80% of chronic neutrophilic leukemia (CNL) patients. Their association with atypical chronic myelogenous leukemia (aCML) remains controversial. They have also been reported as somatic events in severe congenital neutropenia (SCN) patients. There are 2 types of CSF3R mutations: extracellular domain/membrane proximal point mutations (most commonly p.T618I) and cytoplasmic tail truncation mutations. They demonstrated sensitivity to JAK kinase inhibitors and Src kinase inhibitors, respectively, in in vitro assays. In CNL, the most common mutation is p.T618I, although cytoplasmic truncation mutation can also occur. Somatic cytoplasmic truncation mutations have been reported in approximately 30% of SCN patients and 80% of SCN patients with leukemic transformation, who are often on granulocyte-colony stimulating factor (GCSF) therapy. However, their role in leukemic transformation is uncertain.

**Useful For:** Evaluation and classification of chronic neutrophilia Aids in the diagnosis of chronic neutrophilic leukemia (CNL) Identification of mutations that may suggest the class of kinase inhibitor to which the neoplasm may be sensitive

**Interpretation:** The results will be given as positive or negative for CSF3R mutation and, if positive, the mutation will be described.

**Reference Values:**
An interpretive report will be provided

**Clinical References:**

**CTRCZ**

**CTRC Gene, Full Gene Analysis**

**Clinical Information:** Mutations in several genes, including PRSS1, CFTR, CTRC, and SPINK1 have demonstrated genetic susceptibility to chronic pancreatitis. Disease susceptibility may be monogenic, as is the case with PRSS1, digenic, or multigenic, and multifactorial in which multiple genes and environmental factors play a role in disease expression. The most common monogenic cause of hereditary pancreatitis, in which a single gene mutation confers major risk susceptibility to chronic pancreatitis, is the presence of a mutation in the PRSS1 gene. However, mutations in CTRC have also been observed in individuals with chronic pancreatitis in association with other risk factors such as mutations in CFTR or SPINK1 or specific environmental risk factors. Thus, in some cases, chronic pancreatitis may be attributable to the presence of CTRC mutations in the context of other risk factors as opposed to CTRC mutations alone. Genetic testing for all 4 pancreatitis susceptibility genes, including CTRC, is available by ordering HPPAN / Hereditary Pancreatitis Panel.

**Useful For:** Identification of gene mutations contributing to pancreatitis in an individual or family
Identification of gene mutations to allow for predictive/diagnostic testing in family members

**Interpretation:** All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics (AMCG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**CU Index**

**Clinical Information:** Patients with a chronic form of urticaria who are positive (>10) with the CU index have an autoimmune basis for their disease. A positive result does not indicate which autoantibody (anti-IgE, anti-FceRI or anti-FCERII) is present.

**Reference Values:**
< 10.0

The CU Index test is the second generation Functional Anti-FceR test. Patient with a CU Index greater than or equal to 10 have basophil reactive factors in their serum which supports an autoimmune basis for disease.

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**CU Index Panel**

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Thyroid Peroxidase IgG</td>
<td>&lt;35 IU/mL</td>
</tr>
<tr>
<td>Anti-Thyroglobulin IgG</td>
<td>&lt;40 IU/mL</td>
</tr>
<tr>
<td>TSH (Thyrotropin)</td>
<td>0.4 – 4.0 uIU/mL</td>
</tr>
<tr>
<td>CU Index</td>
<td>&lt;10.0</td>
</tr>
</tbody>
</table>

The CU Index test is the second generation Functional Anti-FceR test. Patients with a CU Index greater than or equal to 10 have basophil reactive factors in their serum which supports and autoimmune basis for disease.

---

**Cucumber IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to
select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Cucumber, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
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</tr>
<tr>
<td>5</td>
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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


---

**Cultivated Oat, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>1</td>
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<tr>
<td>2</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
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<td>3</td>
<td>17.5-49.9</td>
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<tr>
<td>5</td>
<td>&gt; or ≥100</td>
<td>Strongly positive</td>
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Reference values apply to all ages.


**CRYE 82918 Cultivated Rye, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


**Cultivated Wheat, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
</tbody>
</table>
5  Strongly positive
50.0-99.9
6  > or =100 Strongly positive Reference values apply to all ages.


**FUNID 8223**

**Culture Referred for Identification, Fungus**

**Clinical Information:** Organisms are referred for identification or to confirm an identification made elsewhere. This may provide helpful information regarding the significance of the organism, its role in the disease process, and its possible origin.

**Useful For:** Identification of pure isolates of filamentous fungi and yeast

**Interpretation:** Genus and species are reported on fungal isolates whenever possible.

**Reference Values:**
Not applicable


**CTBID 80278**

**Culture Referred for Identification, Mycobacterium and Nocardia**

**Clinical Information:** There are over 170 recognized species of mycobacteria and more than 100 Nocardia species. Many of these species are human pathogens and, therefore, identification to the species level is important to help guide patient care. In addition, there are other aerobic actinomycete genera that can be human pathogens including, but not limited to, Tsukamurella, Rhodococcus, and Gordonia species. Nucleic acid hybridization probes are utilized that identify specific ribosomal RNA sequences of Mycobacterium tuberculosis complex, Mycobacterium avium complex, and Mycobacterium gordonae. Other Mycobacteria species, Nocardia species and other aerobic actinomycete genera are identified using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) or nucleic acid sequencing of a 500-base pair region of the 16S ribosomal RNA gene.

**Useful For:** Rapid identification to the species level for Mycobacterium species, Nocardia species, and other aerobic actinomycete genera and species from pure culture isolates

**Interpretation:** Organisms growing in pure culture are identified to the species level whenever possible.

**Reference Values:**
Not applicable

Culture Referred for Identification, Mycobacterium and Nocardia with Antimicrobial Susceptibility Testing

Clinical Information: There are nearly 200 recognized species of mycobacteria and more than 100 Nocardia species. Many are human pathogens and, therefore, identification to the species level is important to help guide patient care. In addition, there are other aerobic actinomycete genera that can be human pathogens including, but not limited to, Tsukamurella, Rhodococcus, and Gordonia species. Nucleic acid hybridization probes are utilized that identify specific ribosomal RNA sequences of Mycobacterium tuberculosis complex, M avium complex, and M gordonae. Other Mycobacteria species, Nocardia species, and other aerobic actinomycete genera are identified using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI TOF MS) or nucleic acid sequencing of a 500-base pair region of the 16S ribosomal RNA gene. After identification, antimicrobial susceptibility testing is performed following Clinical and Laboratory Standards Institute (CLSI) M24 guidelines using either broth dilution or critical concentration methods as appropriate for the species.

Useful For: Rapid identification to the species level and susceptibility testing for Mycobacterium species, Nocardia species, and other aerobic actinomycete genera and species from pure culture isolates

Interpretation: Organisms growing in pure culture are identified to the species level whenever possible.

Reference Values: Not applicable


Culture Referred for Identification, Virus

Clinical Information: Viruses are responsible for a broad spectrum of clinical symptoms and diseases. The most commonly isolated viruses are adenovirus, cytomegalovirus (CMV), enteroviruses, herpes simplex virus (HSV), influenza virus, parainfluenza virus (types 1-3), respiratory syncytial virus (RSV), and varicella-zoster virus (VZV). Some viral infections can be treated with antiviral drugs. Early laboratory diagnosis by isolation may be helpful in the medical management of these patients. Viruses that may be recovered in cell culture include adenovirus, CMV, enterovirus, HSV, VZV, RSV, influenza virus, and parainfluenza virus. HSV and enterovirus are the most commonly recovered viruses. A number of viruses are not routinely detected in cell culture. These include Epstein-Barr virus (EBV), rubella virus (must order serology), human papillomavirus (HPV), Norwalk or norovirus, and West Nile virus.

Useful For: Viral identification and confirmation

Interpretation: A positive result indicates that virus was present in the specimen submitted. Clinical correlation is necessary to determine the significance of the result. Negative results may be seen in a number of situations including absence of viral disease, inability of the virus to grow in culture (examples of organisms not detected by culture include Epstein-Barr virus, rubella virus, human papilloma virus, norovirus and West Nile virus), and nonviable organisms submitted. Parainfluenza virus type 4 also may not be detected by viral culture.

Reference Values: Not applicable

**Curry, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**Reference values apply to all ages.**


---

**Curvularia lunata, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<tr>
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<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
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<td>1 0.35-0.69</td>
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</tr>
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</tr>
</tbody>
</table>

Reference values apply to all ages.


**Curvularia spicifera/Bipolaris IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <.10 Negative 0/1 0.10 â€“ 0.34 Equivocal/Borderline 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 High Positive 4 17.50 â€“ 49.99 Very High Positive 5 50.00 â€“ 99.9 Very High Positive 6 >99.99 Very High Positive

**Reference Values:** <0.35 kU/L

**Cutaneous Anaplastic Large Cell Lymphoma, 6p25.3 (DUSP22 or IRF4) Rearrangement, FISH, Tissue**

**Clinical Information:** Anaplastic lymphoma kinase (ALK)-negative anaplastic large cell lymphoma (ALCL) is a systemic CD30-positive T-cell lymphoma that was included as a provisional entity in the 2008 World Health Organization (WHO) classification of hematopoietic neoplasms. By definition, ALK-negative ALCL resembles ALK-positive ALCL, but lacks ALK protein or ALK gene rearrangements. It affects predominantly adults with a male to female ratio of about 1.5 to 1. ALK-negative ALCL typically involves lymph nodes and sometimes extranodal sites. ALK-negative ALCL must be distinguished clinically from primary cutaneous ALCL, which also is usually
ALK-negative. Recurrent rearrangements of the DUSP22(IRF4) (dual-specificity phosphatase-22, interferon regulatory factor-4) gene locus on 6p25.3 have been described in CD30-positive T-cell lymphomas and lymphoproliferative disorders, including systemic ALK-negative ALCL, primary cutaneous ALCL, and lymphomatoid papulosis. The presence of this rearrangement has potential prognostic significance in ALCL. Specifically, systemic ALK-negative ALCLs with rearrangements of DUSP22(IRF4), but without rearrangements of TP63 on 3q28, have been reported to be associated with favorable clinical outcomes similar to those in systemic ALK-positive ALCL. The frequency of these rearrangements in ALK-negative ALCL was reported to be 30% in a recent series; therefore, absence of a DUSP22(IRF4) rearrangement does not exclude ALK-negative ALCL. Because a similar frequency of this rearrangement has been reported in primary cutaneous ALCL (28% in 1 recent report), the presence of a DUSP22(IRF4) rearrangement does not distinguish between systemic ALK-negative ALCL and primary cutaneous ALCL, and does not eliminate the need for, or take precedence over, collecting a thorough clinical history and staging. This test does not distinguish between rearrangements localized to the DUSP22 gene and those localized to the IRF4 gene. IRF4 rearrangements are seen in rare CD30-negative T-cell lymphomas, a subset of multiple myelomas, and occasional B-cell lymphomas of various subtypes. Clinical utility for demonstrating their presence in these other neoplasms has not been established.

**Useful For:** Providing potentially prognostic information in patients with documented systemic anaplastic lymphoma kinase-negative anaplastic large cell lymphoma

**Interpretation:** Systemic anaplastic lymphoma kinase (ALK)-negative anaplastic large cell lymphoma (ALCL) with rearrangements of DUSP22(IRF4), but without rearrangements of TP63 on 3q28, have been associated with favorable clinical outcomes. Therefore, presence or absence of a TP63 rearrangement needs to be determined to interpret this test accurately. The clinical significance of identifying this rearrangement in cutaneous CD30-positive T-cell lymphoproliferative disorders, including primary cutaneous ALCL and lymphomatoid papulosis, has not been established. Furthermore, other T- and B-lineage neoplasms can demonstrate this finding. Clinical and pathologic correlation is recommended.

A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the DUSP22(IRF4) probe set. A negative result suggests that an DUSP22(IRF4) gene rearrangement is not present, but does not exclude the diagnosis of ALCL.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Cutaneous Direct Immunofluorescence Assay (IFA), Biopsy**

**Clinical Information:** Skin or mucosal tissue from patients with autoimmune bullous diseases, connective tissue disease, vasculitis, lichen planus, and other inflammatory conditions often contains bound immunoglobulin, complement, or fibrinogen. Biopsy specimens are examined for the presence of bound IgG, IgM, IgA, third component of complement (C3), and fibrinogen.

**Useful For:** Confirming a diagnosis of bullous pemphigoid, cicatricial pemphigoid, pemphigoid gestationis and other variants of pemphigoid, all types of pemphigus, including paraneoplastic pemphigus (paraneoplastic multiorgan syndrome), dermatitis herpetiformis, linear IgA bullous dermatosis, chronic bullous disease of childhood, epidermolysis bullosa acquisita, porphyria cutanea tarda, bullous eruption of lupus erythematosus, and atypical or mixed forms of bullous disease, systemic lupus erythematosus, cutaneous lupus erythematosus, or other variants, vasculitis, lichen planus, and other inflammatory diseases. This test is not useful for diagnosis of malignancies involving the skin.
**Interpretation:** A board-certified Dermatopathologist will review and interpret the test results in correlation with other clinical findings as provided.

**Reference Values:**
Report includes description and interpretation of staining patterns.


**Cutaneous Immunofluorescence Antibodies (IgG), Serum**

**Clinical Information:** IgG anti-basement zone (BMZ) antibodies are produced by patients with pemphigoid. In most patients with bullous pemphigoid, serum contains IgG anti-BMZ antibodies, while in cicatricial pemphigoid circulating IgG anti-BMZ antibodies are found in a minority of cases. Sensitivity of detection of anti-BMZ antibodies is increased when serum is tested using sodium chloride (NaCl)-split human skin as substrate. Circulating IgG anti-BMZ antibodies are also detected in patients with epidermolysis bullosa acquisita (EBA) and bullous eruption of lupus erythematosus. IgG anti-cell surface (CS) antibodies are produced by patients with pemphigus. The titer of anti-CS antibodies generally correlates with disease activity of pemphigus. See Method Description for special information pertaining to Herpes gestationis (pemphigoid) and paraneoplastic pemphigus.

**Useful For:** Confirming a diagnosis of pemphigoid, pemphigus, epidermolysis bullosa acquisita, or bullous lupus erythematosus

**Interpretation:** Indirect immunofluorescence (IF) testing may be diagnostic when histologic or direct IF studies are only suggestive, nonspecific, or negative. Anti-cell surface (CS) antibodies correlate with a diagnosis of pemphigus. Anti-basement zone (BMZ) antibodies correlate with a diagnosis of bullous pemphigoid, cicatricial pemphigoid, epidermolysis bullosa acquisita (EBA), or bullous eruption of lupus erythematosus (LE). If serum contains anti-BMZ antibodies, the pattern of fluorescence on sodium chloride(NaCl)-split skin substrate helps distinguish pemphigoid from EBA and bullous LE. Staining of the roof (epidermal side) or both epidermal and dermal sides of NaCl-split skin correlates with the diagnosis of pemphigoid, while fluorescence localized only to the dermal side of the split-skin substrate correlates with either EBA or bullous LE.

**Reference Values:**
Report includes presence and titer of circulating antibodies. If serum contains BMZ antibodies on split-skin substrate, patterns will be reported as: 1) epidermal pattern, consistent with pemphigoid or 2) dermal pattern, consistent with epidermolysis bullosa acquisita.

Negative in normal individuals


**CXCL13 Immunostain, Technical Component Only**

**Clinical Information:** CXCL13 is useful in the classification of nodal T-cell lymphomas with T-follicular helper (TFH) phenotype, and the diagnosis of follicular dendritic cell sarcoma.

**Useful For:** Assessment of CXCL13 expression
**Interpretation:** The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Please contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**CXCR4 Mutation Analysis, Somatic, Lymphoplasmacytic Lymphoma/Waldenstrom Macroglobulinemia**

**Clinical Information:** Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (LPL/WM) is a B-cell lymphoma that is characterized by an aberrant accumulation of malignant lymphoplasmacytic cells in the bone marrow, lymph nodes, and spleen. It is a B-cell neoplasm that can exhibit excess production of serum immunoglobulin-M symptoms related to hyperviscosity, tissue filtration, and autoimmune-related pathology. CXCR4 mutations are identified in approximately 30% to 40% of LPL/WM and are almost always in association with MYD88 L265P, which is highly prevalent in this neoplasm. The status of CXCR4 mutations in the context of MYD88 L265P is clinically relevant as important determinants of clinical presentation, overall survival, and therapeutic response to ibrutinib. A MYD88-L265P/CXCR4-WHIM (C-terminus nonsense/frameshift mutations) molecular signature is associated with intermediate to high bone marrow disease burden and serum IgM levels, less adenopathy, and intermediate response to ibrutinib in previously treated patients; a MYD88-L265P/CXCR4-WT (wild type) molecular signature is associated with intermediate bone marrow disease burden and serum IgM levels, more adenopathy, and highest response to ibrutinib in previously treated patients; and the MYD88-WT/CXCR4-WT molecular signature is associated with inferior overall survival, lower response to ibrutinib therapy in previously treated patients, and lower bone marrow disease burden in comparison to those harboring a MYD88-L265 mutation. This test is used to aid in the prognostication and therapeutic management of LPL/WM.

**Useful For:** Prognostication and clinical management of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia

**Interpretation:** Mutations detected or not detected. An interpretive report will be issued.

**Reference Values:**
Mutations present or absent in the test region of the CXCR4 gene (NCBI NM_003467.2, GRCh37).

Cyanide, Blood Test

Reference Values:
Normal: Up to 0.05 mcg/mL  
Potentially toxic: 0.50 mcg/mL and greater  
Potentially lethal: 2.0 mcg/mL and greater

Cyclic AMP, Urinary Excretion

Clinical Information: Cyclic AMP functions as an intracellular "second messenger" regulating the activity of intracellular enzymes or proteins in response to a variety of hormones (eg, parathyroid hormone). Urinary cyclic AMP is elevated in about 85% of patients with hyperparathyroidism.

Useful For: Differential diagnosis of hypercalcemia  
Adjunct to serum parathyroid hormone measurements, especially in the diagnosis of parathyroid hormone resistance states, such as pseudohypoparathyroidism

Interpretation: Urinary cyclic AMP is elevated in about 85% of patients with hyperparathyroidism and in about 50% of patients with humoral hypercalcemia of malignancy.

Reference Values:
1.3-3.7 nmol/dL of glomerular filtrate


Cyclic Citrullinated Peptide Antibodies, IgG, Serum

Clinical Information: Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic joint inflammation that ultimately leads to joint destruction. RA affects approximately 1% of the world's population. The diagnosis of RA is established primarily on clinical criteria and serologic findings. Historically, rheumatoid factor (RF), which is an antibody specific for the Fc portion of human IgG, has been considered a marker for RA. RF is, in fact, one of the diagnostic criteria for RA that was established by the American College of Rheumatology. (1) Although 50% to 90% of patients with RA are RF-positive, the specificity of the RF test is known to be relatively poor. RF is found in many patients with other autoimmune diseases, infectious diseases and some healthy individuals. Consequently, a search for better diagnostic markers, with improved specificity for RA, ensued. Antiperinuclear factor (APF) and antikeratin antibodies (AKA), identified by immunofluorescence, were found to have a specificity of close to 90% for RA, but testing for these autoantibodies has never become popular. It was subsequently determined that APF and AKA react with the same antigen, specifically a citrullinated form of filaggrin (citrulline is an unusual amino acid formed by posttranslational modification of arginine residues by the enzyme peptidyl arginine deaminase). (2) Recombinant filaggrin fragments, after enzymatic deamination in vitro, react with autoantibodies in RA sera. Synthetic cyclic citrullinated peptide (CCP) variants also react with anti-filaggrin autoantibodies and serve as the substrate for detecting anti-CCP antibodies serologically. Most studies of anti-CCP antibodies demonstrated that these autoantibodies have much improved specificity for RA compared to RF. (3) See Connective Tissue Diseases Cascade (CTDC) in Special Instructions.

Useful For: Evaluating patients suspected of having rheumatoid arthritis (RA)  
Differentiating RA from other connective tissue diseases that may present with arthritis

Interpretation: A positive result for cyclic citrullinated peptide (CCP) antibodies indicates a high likelihood of rheumatoid arthritis (RA). A Mayo prospective clinical evaluation of the CCP antibody
test showed a diagnostic sensitivity for RA of 78% with fewer than 5% false positive results in healthy controls (see Cautions). CCP antibodies have also been reported in approximately 40% of seronegative RA patients, and, like rheumatoid factor (RF), a positive CCP antibody result indicates an increased likelihood of erosive disease in patients with RA. High levels of CCP antibodies may be useful to identify patients with aggressive disease, but further studies are needed to document this association. The level of CCP antibodies may also correlate with disease activity in RA, but further studies are needed to document this clinical application.

Reference Values:

<table>
<thead>
<tr>
<th>Value</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20.0 U</td>
<td>(negative)</td>
</tr>
<tr>
<td>20.0-39.9 U</td>
<td>(weak positive)</td>
</tr>
<tr>
<td>40.0-59.9 U</td>
<td>(positive)</td>
</tr>
<tr>
<td>&gt; or =60.0 U</td>
<td>(strong positive)</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

Clinical References:

Cyclin D1 (CCND1, CYCD1) Immunostain, Technical Component Only

Clinical Information:
Cyclin D1 is a protein that regulates entry of the cell into cell cycle. It drives the transition between G0 and G1 phase. In normal tissues, basal epithelial cells, endothelial cells, and stromal cells are often cyclin D1 positive, as these cells are going through the cell cycle. As a result of a translocation involving the cyclin D1 gene and IgH, t(11;14), the vast majority of mantle cell lymphomas overexpress cyclin D1. This is a useful feature in the classification of low-grade B-cell lymphomas.

Useful For: Classification of low-grade B-cell lymphomas

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:
**Cyclospora Stain**

**Clinical Information:** Cyclospora cayetanensis is an apicomplexan protozoan parasite that causes watery diarrhea, anorexia, malaise, and weight loss. The extent of symptoms depends on the age and condition of the host and the infectious dose. The infection is usually self-limited, but symptoms can be severe and prolonged, particularly in immunocompromised patients. Cyclosporal diarrheal disease is endemic in many parts of the world, including Asia, India, Southeast Asia, and Latin America. Although most cases of cyclosporiasis have been seen in travelers to developing countries, outbreaks in the United States have been noted due to contaminated fruits and vegetables from Latin America. Transmission is via fecally contaminated food or water. If untreated, symptoms typically last for 10 to 12 weeks, and may follow a relapsing course. The infection usually responds to treatment with a sulfamethoxazole-trimethoprim drug combination. Cyclospora cayetanensis oocysts are traditionally detected by modified acid-fast staining, in which the oocysts stain bright pink-red. However, the modified safranin stain has been shown to provide increased sensitivity over modified acid-fast method and produces a more rapid result. It is the method used in our laboratory to detect Cyclospora cayetanensis oocysts in fecal sediment. See Laboratory Testing for Infectious Causes of Diarrhea and Parasitic Investigation of Stool Specimens Algorithm for other diagnostic tests that may be of value in evaluating patients with diarrhea.

**Useful For:** The identification of Cyclospora cayetanensis as a cause of infectious gastroenteritis

**Interpretation:** A report of Cyclospora cayetanensis detected indicates the presence of this parasite in the patient's feces.

**Reference Values:**
Negative
If positive, reported as Cyclospora cayetanensis detected.


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**Cyclosporine, Blood**

**Clinical Information:** Cyclosporine is a lipophilic polypeptide used to prevent rejection after solid organ transplantation; it suppresses T-cell activation by inhibiting calcineurin to decrease interleukin-2 (IL-2) production. There is substantial interpatient variability in absorption, half-life, and other pharmacokinetic parameters. Cyclosporine is extensively metabolized by CYP3A4 to at least 30 less-active metabolites, many of which are detected by immunoassays. Cyclosporine is known for many drug interactions, including increased neuro- and nephrotoxicity when coadministered with antibiotics, antifungals, or other immunosuppressants. Cyclosporine has a narrow therapeutic range with frequent adverse effects making therapeutic drug monitoring essential. With 80% of cyclosporine sequestered in erythrocytes, whole blood is the preferred specimen for analysis. Dose is adjusted initially (up to 2 months posttransplant) to maintain concentrations generally between 150 and 400 ng/mL. Target trough concentrations vary according to clinical protocol and depend on type of allograft, risk of rejection, concomitant immunosuppressive drugs, and toxicity. After the first 2 postoperative months, the target range is generally lower, between 75 and 300 ng/mL. Conversion between formulations is generally done at the same dose but with drug monitoring.

**Useful For:** Monitoring whole blood cyclosporine concentration during therapy, particularly in individuals coadministered CYP3A4 substrates, inhibitors, or inducers Adjusting dose to optimize immunosuppression while minimizing toxicity Evaluating patient compliance
**Interpretation:** Most individuals display optimal response to cyclosporine with trough whole blood levels 100 to 400 ng/mL. Preferred therapeutic ranges may vary by transplant type, protocol, and comedications. Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next scheduled dose). Blood drawn at other times will yield higher results. This test may also be used to analyze cyclosporine levels 2 hours after dosing (C2 concentrations); trough therapeutic ranges do not apply to C2 specimens. The assay is specific for cyclosporine; it does not cross-react with cyclosporine metabolites, sirolimus, sirolimus metabolites, tacrolimus, or tacrolimus metabolites. Results by liquid chromatography with detection by tandem mass spectrometry are approximately 30% less than by immunoassay.

**Reference Values:**
100-400 ng/mL (Trough)

Target steady-state trough concentrations vary depending on the type of transplant, concomitant immunosuppression, clinical/institutional protocols, and time post-transplant. Results should be interpreted in conjunction with this clinical information and any physical signs/symptoms of rejection/toxicity.

**Clinical References:**

**Cyclosporine, Peak, Blood**

**Clinical Information:** Cyclosporine is a lipophilic polypeptide used to prevent rejection after solid organ transplantation; it suppresses T-cell activation by inhibiting calcineurin to decrease interleukin-2 (IL-2) production. There is substantial interpatient variability in absorption, half-life, and other pharmacokinetic parameters. Cyclosporine is extensively metabolized by CYP3A4 to at least 30 less-active metabolites, many of which are detected by immunoassays. Cyclosporine is known for many drug interactions, including increased neuro- and nephrotoxicity when coadministered with antibiotics, antifungals, or other immunosuppressants. Cyclosporine has a narrow therapeutic range with frequent adverse effects making therapeutic drug monitoring essential. With 80% of cyclosporine sequestered in erythrocytes, whole blood is the preferred specimen for analysis.

**Useful For:** Monitoring whole blood cyclosporine concentration during therapy, particularly in individuals coadministered CYP3A4 substrates, inhibitors, or inducers Adjusting dose to optimize immunosuppression while minimizing toxicity Evaluating patient compliance

**Interpretation:** No definitive therapeutic or toxic ranges have been established for postdose peak monitoring. Preferred therapeutic ranges may vary by transplant type, protocol, and comedications. The 2-hour postdose cyclosporine ranges listed for this test are only suggested guidelines. This assay is specific for cyclosporine; it does not cross-react with cyclosporine metabolites, sirolimus, sirolimus metabolites, tacrolimus, or tacrolimus metabolites. Results by liquid chromatography with detection by tandem mass spectrometry are approximately 30% less than by immunoassay.

**Reference Values:**
No definitive therapeutic or toxic ranges have been established.

Optimal blood drug levels are influenced by type of transplant, patient response, time posttransplant, coadministration of other drugs, and drug formulation.

The following 2-hour postdose cyclosporine ranges are only suggested guidelines:
Renal transplant: 800-1700 ng/mL  
Liver transplant: 600-1000 ng/mL
Target steady-state peak concentrations vary depending on the type of transplant, concomitant immunosuppression, clinical/institutional protocols, and time posttransplant. Results should be interpreted in conjunction with this clinical information and any physical signs/symptoms of rejection/toxicity.


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**3A5V**

**Clinical Information:**

CYP3A5 is a member of the CYP3A family of genes located on chromosome 7. The CYP3A subfamily of enzymes responsible for the metabolism of more than 50% of medications that undergo hepatic metabolism and first-pass metabolism in intestinal epithelial cells. The CYP3A5 expression level and enzymatic activity can be modulated by genetic variation. CYP3A5 allelic frequency depends upon ethnicity. For example, in individuals of European descent the most common allele is the CYP3A5*3 allele (c.219-237A>G), which results in a splicing defect and absence of enzyme activity. In individuals of African descent, the *1 allele (functional enzyme) is most common. The distribution of CYP3A5*3 allele frequencies ranges from 0.14 among sub-Saharan Africans to 0.95 in European populations. In general, most drugs metabolized by CYP3A5 are also metabolized by CYP3A4 and usually to a greater degree than CYP3A5. For this reason, substrates of these 2 enzymes are sometimes listed together in publications and genotyping of both genes might be needed to fully understand the metabolism of these drugs and predict phenotype. If CYP3A4 genotyping is needed, order 3A4V / Cytochrome P450 3A4 Genotype. CYP3A5 testing is commonly ordered for patients receiving tacrolimus. Tacrolimus is an immunosuppressive calcineurin inhibitor used in transplant recipients. Tacrolimus has a low therapeutic index with a wide range of side effects and large interindividual variability in its pharmacokinetics, particularly in the dose required to reach target trough blood concentrations, thus necessitating routine therapeutic drug monitoring in clinical practice. Tacrolimus dose requirements are most closely associated with CYP3A5 genotype even though the drug is metabolized by both CYP3A4 and CYP3A5. According to existing literature and Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, individuals with at least 1 copy of fully functional CYP3A5 (ie, *1/*1 and *1/*3) require a higher dose of tacrolimus to reach the targeted whole blood concentrations than those without a copy of a fully functional CYP3A5 allele (ie, *3/*3). CYP3A5 genotyping may predict dose requirements for tacrolimus, but does not replace the need for therapeutic monitoring to guide tacrolimus dose adjustments. For a patient with the CYP3A5*3/*3 genotype, initiating tacrolimus therapy with a standard (normal) dose is recommended. One of the complications in interpreting CYP3A5 genotyping results and the effect of genotype on drug dosing is the fact that most individuals involved in drug trials have been of European decent. Individuals of European decent are more likely to have the CYP3A5*3/*3 genotype, which predicts a poor metabolizer phenotype. Dosing requirements were derived from these clinical trials so individuals with 1 or 2 copies of CYP3A5*1, will functionally behave like rapid or ultrarapid metabolizers and may require higher doses of CYP3A5 metabolized drugs. The following table displays the CYP3A5 variants detected by this assay, the corresponding star allele, and the effect on CYP3A5 enzyme activity:

<table>
<thead>
<tr>
<th>CYP3A5 Allele</th>
<th>cDNA Nucleotide Change</th>
<th>Effect on Enzyme Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1 None (wild type)</td>
<td>Normal activity</td>
<td>*1 None (wild type)</td>
</tr>
<tr>
<td>*3 219-237A-&gt;G No activity</td>
<td>*3 219-237A-&gt;G No activity</td>
<td></td>
</tr>
<tr>
<td>*4 432+2T-&gt;C No activity</td>
<td>*4 432+2T-&gt;C No activity</td>
<td></td>
</tr>
<tr>
<td>*5 624G-&gt;A Reduced activity</td>
<td>*5 624G-&gt;A Reduced activity</td>
<td></td>
</tr>
<tr>
<td>*6 1035dup No activity</td>
<td>*6 1035dup No activity</td>
<td></td>
</tr>
<tr>
<td>*7 82C-&gt;T Reduced activity</td>
<td>*7 82C-&gt;T Reduced activity</td>
<td></td>
</tr>
<tr>
<td>*9 1009G-&gt;A Reduced activity</td>
<td>*9 1009G-&gt;A Reduced activity</td>
<td></td>
</tr>
</tbody>
</table>

**Useful For:** Aids in optimizing treatment with tacrolimus and other drugs metabolized by CYP3A5

**Interpretation:** An interpretive report will be provided. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by Pharmacogene Variation (PharmVar) Consortium.(1) For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables in Special Instructions. This resource also
includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Cystatin C with Estimated GFR, Serum**

**Clinical Information:** Cystatin C: Cystatin C is a low molecular weight (13,250 kD) cysteine proteinase inhibitor that is produced by all nucleated cells and found in body fluids, including serum. Since it is formed at a constant rate and freely filtered by the kidneys, its serum concentration is inversely correlated with the glomerular filtration rate (GFR); that is, high values indicate low GFRs while lower values indicate higher GFRs, similar to creatinine. The renal handling of cystatin C differs from creatinine. While both are freely filtered by glomeruli, once it is filtered, cystatin C, unlike creatinine, is reabsorbed and metabolized by proximal renal tubules. Thus, under normal conditions, cystatin C does not enter the final excreted urine to any significant degree. The serum concentration of cystatin C remains unchanged with infections, inflammatory or neoplastic states, and is not affected by body mass, diet, or drugs. Thus, cystatin C may be a more reliable marker of renal function (GFR) than creatinine. Estimated Glomerular Filtration Rate (GFR): GFR can be estimated (eGFR) from serum cystatin C utilizing an equation which includes the age and gender of the patient. The CKD-EPI cystatin C equation was developed by Inker et al:(1) and demonstrated good correlation with measured iothalamate clearance in patients with all common causes of kidney disease, including kidney transplant recipients. Cystatin C eGFR may have advantages over creatinine eGFR in certain patient groups in whom muscle mass is abnormally high or low (for example quadriplegics, very elderly, or malnourished individuals). Blood levels of cystatin C also equilibrate more quickly than creatinine, and therefore, serum cystatin C may be more accurate than serum creatinine when kidney function is rapidly changing (for example amongst hospitalized individuals).

**Useful For:** Cystatin C: An index of glomerular filtration rate, especially in patients where serum creatinine may be misleading (eg, very obese, elderly, or malnourished patients) Assessing renal function in patients suspected of having kidney disease Monitoring treatment response in patients with kidney disease Estimated Glomerular Filtration Rate (eGFR): An index of GFR, especially in patients where serum creatinine may be misleading (eg, very obese, elderly, or malnourished patients); for such patients, use of CKD-EPI cystatin C equation is recommended to estimate GFR Assessing renal function in patients suspected of having kidney disease Monitoring treatment response in patients with kidney disease

**Interpretation:** Cystatin C: Cystatin C inversely correlates with the glomerular filtration rate (GFR), that is elevated levels of cystatin C indicate decreased GFR. Cystatin C may provide more accurate assessment of GFR for very obese, elderly, or malnourished patients than creatinine. Cystatin C equation does not require patient ethnic data, and can be used for those patients with this information unavailable. Due to immaturity of renal function, cystatin C levels are higher in neonates <3 months of age.(2) Estimated Glomerular Filtration Rate (eGFR): Chronic kidney disease (CKD) is defined as the presence of persistent and usually progressive reduction in GFR (GFR <60 mL/min/1.73 m2) and/or albuminuria (>30 mg of urinary albumin per gram of urinary creatinine), regardless of GFR. According to the National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) classification, among patients with CKD, irrespective of diagnosis, the stage of disease should be assigned based on the level of kidney function: Stage Description GFR mL/min/BSA 1 Kidney damage with normal or increased GFR 90 2 Kidney damage with mild decrease in GFR 60-89 3 Moderate decrease in GFR 30-59 4 Severe decrease in GFR 15-29 5 Kidney failure <15 (or dialysis)
Reference Values:

CYSTATIN C

Males:
- 0 days-22 years: no reference values established
- 23-29 years: 0.60-1.03 mg/L
- 30-39 years: 0.64-1.12 mg/L
- 40-49 years: 0.68-1.22 mg/L
- 50-59 years: 0.72-1.32 mg/L
- 60-69 years: 0.77-1.42 mg/L
- 70-79 years: 0.82-1.52 mg/L
- >79 years: no reference values established

Females:
- 0 days-22 years: no reference values established
- 23-29 years: 0.57-0.90 mg/L
- 30-39 years: 0.59-0.98 mg/L
- 40-49 years: 0.62-1.07 mg/L
- 50-59 years: 0.64-1.17 mg/L
- 60-69 years: 0.66-1.26 mg/L
- 70-80 years: 0.68-1.36 mg/L
- 81-86 years: 0.70-1.45 mg/L
- >86 years: no reference values established

eGFR

>60 mL/min/BSA
eGFR will not be calculated for patients under 18 years.

Clinical References:

Cystic Fibrosis Mutation Analysis, 106-Mutation Panel

Clinical Information: Cystic fibrosis (CF), in the classic form, is a severe autosomal recessive disorder characterized by a varied degree of chronic obstructive lung disease and pancreatic enzyme insufficiency. The incidence of CF varies markedly among different populations, as does the mutation detection rate for the mutation screening assay. To date, over 1,500 mutations have been described within the CF gene, named cystic fibrosis transmembrane conductance regulator (CFTR). The most common mutation, deltaF508, accounts for approximately 67% of the mutations worldwide and approximately 70% to 75% in a North American Caucasian population. Most of the remaining mutations are rather rare, although some show a relatively higher prevalence in certain ethnic groups or in some atypical presentations of CF such as congenital bilateral absence of the vas deferens (CBAVD).
Mutations detected by the assay performed in the Mayo Clinic Molecular Genetics Laboratory include the 23 mutations recommended by the American College of Medical Genetics as well as 83 other mutations. Of note, CFTR potentiator therapies may improve clinical outcomes for patients with a clinical diagnosis of CF and at least 1 copy of the G178R, G551S, G551D, S549N, S549R, G1244E, S1251N, S1255P, or G1349D mutation. The G178R, S549N, S549R, S551D, and S1251N mutations are included in this test. These 106 mutations account for approximately 91% of CF chromosomes in a Northern European Caucasian population. Detection rates for several ethnic and racial groups are listed in the table below. Note that interpretation of test results and risk calculations are also dependent on clinical information and family history. Racial or Ethnic Group Carrier Frequency Mutation Detection Rate* African American 1/65 81% Ashkenazi Jewish 1/25 97% Asian American (excluding individuals of Japanese ancestry) 1/90 54% Mixed European 1/25 82% Eastern European 1/25 77% French Canadian 1/25 91% Hispanic American 1/46 82% Northern European 1/25 91% Southern European 1/25 79% *Rates are for classical CF. Rates are lower for atypical forms of CF and for CBAVD. CFTR mutations listed below are included in this panel. Deletion exons 2-3 Exon 11: R553X Exon 21: 4016insT Exon 11: G551D Exon 21: N1303K (C->A) Exon 11: Q552X Exon 21: N1303K (C->G) See Cystic Fibrosis Molecular Diagnostic Testing Algorithm in Special Instructions for additional information.

Useful For: Confirmation of a clinical diagnosis of cystic fibrosis Risk refinement via carrier screening for individuals in the general population Prenatal diagnosis or familial mutation testing when the familial mutations are included in the 106-mutation panel listed above (if familial mutations are not included in the 106-mutation panel, order FMTT / Familial Mutation, Targeted Testing) Risk refinement via carrier screening for individuals with a family history when familial mutations are not available Identification of patients who may respond to CFTR potentiator therapy

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.


**Cysticercosis Antibody, IgG by ELISA**

**Interpretation:** Seroconversion between acute and convalescent sera is considered strong evidence of recent infection. The best evidence for infection is a significant change on two appropriately timed specimens where both tests are done in the same laboratory at the same time. Patients with collagen vascular diseases, hepatic cirrhosis, schistosomiasis, and other parasitic infections can produce false-positive results. There is a strong cross-reaction between cysticercosis and echinococcosis positive sera. Confirmation of positive ELISA results by the cysticercosis antibody, IgG by Western blot is recommended.

**Reference Values:**
Reference Interval: <=0.34 O.D.

- 0.34 O.D. or less: Negative- No significant level of cysticercosis IgG antibody detected.
- 0.35-0.50 O.D.: Equivocal- Questionable presence of cysticercosis IgG antibody detected. Repeat testing in 10-14 days may be helpful.
- 0.51 O.D. or greater: Positive- IgG antibody to cysticercosis detected, which may suggest current or past infection.

**Cysticercus Antibody, ELISA (CSF)**

**Clinical Information:** Cysticercosis is caused by infection with the larval form (cysticercus) of the pork tapeworm, Taenia solium. A negative test result does not exclude the diagnosis of neurocysticercosis, particularly if only a single brain lesion is present. Test sensitivity increases from 50% or less for a solitary brain cyst to greater than 90% if 3 or more cysts are present. Antibodies from other parasitic infection, particularly results by the cysticercus IgG antibody Western blot is thus recommended.

**Reference Values:**
Reference Range: <0.75

Interpretive Criteria:

- <0.75 Antibody Not Detected
- > or = 0.75 Antibody Detected

Diagnosis of central nervous system infections can be accomplished by demonstrating the presence of intrathecally-produced specific antibody. Interpretation of results may be complicated by low antibody levels found in CSF, passive transfer of antibody from blood, and contamination via bloody taps.

Antibodies to other parasitic infections, particularly echinococcosis, may crossreact in the cysticercus IgG ELISA. Confirmation of positive ELISA results by the cysticercus IgG antibody Western blot is thus recommended.
Clinical Information: Cystinuria is an inborn error of metabolism resulting from poor absorption and reabsorption of the amino acid cystine in the intestine and in the kidney. This leads to an accumulation of poorly soluble cystine in the urine and results in the production of kidney stones (urolithiasis). Symptoms may include acute episodes of abdominal or lower back pain, presence of blood in the urine (hematuria), and recurrent episodes of kidney stones may result in frequent urinary tract infections, which may ultimately result in renal insufficiency. The combined incidence of cystinuria has been estimated to be 1 in 7,000. Cystinuria can be classified into 3 subtypes based on the excretion of amino acids in the urine of heterozygotes (parents or children of affected individuals). Heterozygotes of type I excrete normal amounts of cystine, while those with types II and III present with slight to moderate excretion of cystine and other amino acids (lysine, arginine, and ornithine). All 3 subtypes are caused by mutations in only 2 genes, SLC3A1 on chromosome 2p and SLC7A9 on chromosome 19q. A new classification system has been proposed to distinguish the various forms of cystinuria: type A, due to mutations in the SLC3A1 gene; type B, due to mutations in the SLC7A9 gene; and type AB, due to 1 mutation in each SLC3A1 and SLC7A9.

Useful For: Diagnosis of cystinuria

Interpretation: Homozygotes or compound heterozygotes with cystinuria excrete large amounts of cystine in urine, but the amount varies markedly. Urinary excretion of other dibasic amino acids (arginine, lysine, and ornithine) are also typically elevated. Plasma concentrations are generally normal or slightly decreased. Individuals who are homozygous and heterozygous for non-type I cystinuria can be distinguished by the pattern of urinary amino acids excretion: the former secretes large amounts of cystine and all 3 dibasic amino acids, whereas the latter secretes more lysine and cystine than arginine and ornithine.

Reference Values:

CYSTINE
3-15 years: 11-53 mcmol/24 hours
> or =16 years: 28-115 mcmol/24 hours

LYSINE
3-15 years: 19-140 mcmol/24 hours
> or =16 years: 32-290 mcmol/24 hours

ORNITHINE
3-15 years: 3-16 mcmol/24 hours
> or =16 years: 5-70 mcmol/24 hours

ARGININE
3-15 years: 10-25 mcmol/24 hours
> or =16 years: 13-64 mcmol/24 hours

Conversion Formulas:
Result in mcmol/24 hours x 0.24=result in mg/24 hours
Result in mg/24 hours x 4.17=result in mcmol/24 hours


CYSR 81067

Cystinuria Profile, Quantitative, Random, Urine

Clinical Information: Cystinuria is an inborn error of metabolism resulting from poor absorption and reabsorption of the amino acid cystine in the intestine and in the kidney. This leads to an accumulation of poorly soluble cystine in the urine and results in the production of kidney stones (urolithiasis). Symptoms may include acute episodes of abdominal or lower back pain, presence of blood in the urine (hematuria),
and recurrent episodes of kidney stones may result in frequent urinary tract infections, which may ultimately result in renal insufficiency. The combined incidence of cystinuria has been estimated to be 1 in 7,000. Cystinuria can be classified into 3 subtypes based on the excretion of amino acids in the urine of heterozygotes (parents or children of affected individuals). Heterozygotes of type I excrete normal amounts of cystine, while those with types II and III present with slight-to-moderate excretion of cystine and other amino acids (lysine, arginine, and ornithine). All 3 subtypes are caused by mutations in only 2 genes, SLC3A1 on chromosome 2p and SLC7A9 on chromosome 19q. A new classification system has been proposed to distinguish the various forms of cystinuria: type A, due to mutations in the SLC3A1 gene; type B, due to mutations in the SLC7A9 gene; and type AB, due to 1 mutation in each SLC3A1 and SLC7A9.

**Useful For:** Biochemical diagnosis and monitoring of cystinuria

**Interpretation:** Homozygotes or compound heterozygotes with cystinuria excrete large amounts of cystine in urine, but the amount varies markedly. Urinary excretion of other dibasic amino acids (arginine, lysine, and ornithine) is also typically elevated. Plasma concentrations are generally normal or slightly decreased. Individuals who are homozygous and heterozygous for non-type I cystinuria can be distinguished by the pattern of urinary amino acids excretion: homozygous individuals secrete large amounts of cystine and all 3 dibasic amino acids, whereas heterozygous individuals secrete more lysine and cystine than arginine and ornithine.

**Reference Values:**

<table>
<thead>
<tr>
<th>Urine Amino Acid Reference Values (nmol/mg creatinine)</th>
<th>Age Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; or =12 Months</td>
</tr>
<tr>
<td></td>
<td>(n=36)</td>
</tr>
<tr>
<td>Arginine Arg</td>
<td>10-560</td>
</tr>
<tr>
<td>Ornithine Orn</td>
<td>12-504</td>
</tr>
</tbody>
</table>

**Clinical References:**

**Cytochrome Oxidase Stain (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

Order MPCT / Muscle Pathology Consultation or MBCT / Muscle Biopsy Consultation, Outside Slides and/or Paraffin Blocks. The consultant will determine the need for special stains.

**Cytochrome P450 1A2 Genotype**

**Clinical Information:** The cytochrome P450 (CYP) family is involved in the primary metabolism of many drugs. The CYPs are a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of these CYP enzymes, CYP1A2, is wholly or partially responsible for the hydroxylation or dealkylation of many commonly prescribed drugs.
CYP1A2-mediated drug metabolism is highly variable. A number of variants have been identified in the CYP1A2 gene that results in increased, diminished, or abolished catalytic activity and substrate metabolism. The frequency of these variants varies by ethnicity. Dosing of drugs that are metabolized through CYP1A2 may require adjustment based on the CYP1A2 genotype. Individuals who are poor metabolizers may require lower than usual doses to achieve optimal response, whereas individuals who are ultrarapid metabolizers may benefit from increased doses. CYP1A2 phenotype is predicted based upon the number of functional, partially functional, nonfunctional, and inducible alleles present in a sample. In the absence of clear guidance on dosing for various metabolizer phenotypes, patients with either rapid or poor metabolism also may benefit by switching to another comparable drug that is not primarily metabolized by CYP1A2 or by therapeutic drug monitoring where applicable. The following table outlines the relationship between the variations (star alleles) detected in this assay and the effect on the activity of the enzyme produced by that allele. CYP1A2 Allele Nucleotide Change (Legacy nomenclature) cDNA Nucleotide Change Effect on Enzyme Metabolism(a) *1 None (wild type) None (wild type) Normal (extensive) metabolizer *1F -163C->A c.-9-154C->A Increased inducibility *1K -729C->T c.-10+113C->T Decreased activity and decreased inducibility *6 5090C->T c.1291C->T No activity *7 3533G->A c.1253+1G->A No activity a. Effect of a specific allele on the activity of the CYP1A2 enzyme can only be estimated since the literature does not provide precise data. A complicating factor in correlating CYP1A2 genotype to CYP1A2 phenotype is that some drugs or their metabolites are inhibitors of CYP1A2 catalytic activity. These drugs may reduce CYP1A2 catalytic activity. Consequently, an individual may require a dose decrease greater than predicted based upon genotype alone. Another complicating factor is that CYP1A2 is inducible by several drugs and environmental agents (eg, cigarette smoke) and the degree of inducibility is under genetic control. It is important to interpret the results of testing in the context of other coadministered drugs and environmental factors.

Useful For: Identifying individuals who are poor, intermediate, normal (extensive) or rapid metabolizers of drugs metabolized by CYP1A2 to assist drug therapy decision making

Interpretation: An interpretive report will be provided. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Pharmacogene Variation (PharmVar) Consortium.(1) CYP1A2 activity is also dependent upon hepatic function status, as well as age. Renal function may be important for drugs that are excreted in urine. Patients may develop drug toxicity if hepatic or renal function is decreased. Drug metabolism is known to decrease with age. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and age. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
An interpretive report will be provided.


2C19V 97390

Cytochrome P450 2C19 Genotype

Clinical Information: Primary metabolism of many drugs is performed by the cytochrome P450 (CYP450) enzymes, a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of these CYP450 enzymes, CYP2C19, participates in the metabolism of a wide variety of drugs, including the activation of the anticoagulant clopidogrel and the inactivation of citalopram. CYP2C19 drug metabolism is variable among individuals. Some individuals...
have CYP2C19 genetic variants that lead to severely diminished or absent CYP2C19 catalytic activity (i.e., poor metabolizers). The frequency of CYP2C19 variants (also referred to as polymorphisms) depends on ethnicity. CYP2C19 variants that produce poor metabolizers are found with frequencies of 2% to 5% in Caucasians, 4% in African Americans, 13% to 23% in Asians, and 38% to 79% in Polynesians and Micronesians. The following table displays the CYP2C19 variants detected by this assay, the corresponding star allele, and the effect on CYP2C19 enzyme activity: CYP2C19 Allele cDNA Nucleotide Change Effect on Enzyme Activity *1 None (wild type) Normal (extensive) activity *2 681G->A No activity *3 636G->A No activity *4 1A->G No activity *5 1297C->T No activity *6 395G->A No activity *7 819+2T->A No activity *8 358T->C No activity *9 431G->A Decreased activity *10 680C->T Minimal activity *17 -806C->T Enhanced activity *35 332-23A->G in the absence of 681G->A No activity CYP2C19 drug metabolism is dependent on the specific genotype detected and also on the number and type of drugs administered to the patient. Individuals without a detectable CYP2C19 variant will have the predicted phenotype of an extensive drug metabolizer and are designated as CYP2C19 *1/*1. If an individual is homozygous or compound heterozygous for alleles with no activity, the individual is predicted to be a poor metabolizer. If an individual is heterozygous for an allele with no activity, the individual is predicted to be an intermediate metabolizer. Individuals with the CYP2C19*17 allele (in the absence of any inactive or decreased activity alleles) may have enhanced metabolism of drugs. In some cases, a range of potential phenotypes may be given, depending on the combination of alleles identified. Patients who are poor metabolizers may benefit from dose alteration or selection of a comparable drug that is not primarily metabolized by CYP2C19. It is important to interpret the results of testing in the context of other coadministered drugs.

Useful For: Identifying patients who may be at risk for altered metabolism of drugs that are modified by CYP2C19 Predicting anticoagulation response to clopidogrel

Interpretation: An interpretive report will be provided. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Pharmacogene Variation (PharmVar) Consortium.(1) For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices. Drug-drug interactions and drug-metabolite inhibition must be considered when treating intermediate metabolizers. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and patient age.

Reference Values: An interpretive report will be provided.


Cytochrome P450 2C9 Genotype

Clinical Information: Primary metabolism of many drugs is performed by the cytochrome P450 (CYP450) enzymes, a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues, but primarily in the intestines and liver. One of these CYP450 enzymes, CYP2C9, participates in the metabolism of a wide variety of drugs including warfarin and phenytoin. CYP2C9-mediated drug metabolism is variable among individuals. Some individuals have CYP2C9 genetic variants that lead to severely diminished or absent CYP2C9 catalytic activity (i.e., poor metabolizers). These individuals may metabolize various drugs at a slower rate than normal and may require dosing adjustments to prevent adverse drug reactions. A number of specific CYP2C9 variants have been identified that result in
enzymatic deficiencies. The following information outlines the relationship between the variants detected in the assay and their effect on enzyme activity: CYP2C9 Allele cDNA Nucleotide Change Effect on Enzyme Metabolism

*1 None (wild type) Normal activity
*2 430C->T Reduced activity
*3 1075A->C No activity
*4 1076T->C Reduced activity
*5 1080C->G Reduced activity
*6 818delA No activity
*7 449G->A Substrate specific
*8 752A->G Reduced activity
*9 1003C->T Reduced activity
*10 1465C->T Reduced activity
*11 269C->T Minimal activity
*12 374G->A Minimal activity
*13 485C->A No activity
*14 895A->G Minimal activity
*15 1144C->T Reduced activity
*16 1190A->C Minimal activity
*17 353_362del No activity
*18 389C->G Minimal activity

CYP2C9 drug metabolism is dependent on the specific genotype detected, and also on the number and type of drugs administered to the patient. Individuals without a detectable CYP2C9 variant will have the predicted phenotype of an extensive drug metabolizer and are designated as CYP2C9 *1/*1. If an individual is homozygous or compound heterozygous for an allele with no activity, the individual is predicted to be a poor metabolizer. If an individual is heterozygous for an allele with no activity, the individual is predicted to be an intermediate metabolizer. In some cases, a range of potential phenotypes may be given, depending on the combination of alleles identified. Patients who are poor metabolizers may benefit from dose alteration or selection of a comparable drug that is not primarily metabolized by CYP2C9. It is important to interpret the results of testing in the context of other coadministered drugs.

**Useful For:** Identifying individuals who may be at risk for altered metabolism of drugs that are modified by CYP2C9

**Interpretation:** An interpretive report will be provided. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Pharmacogene Variation (PharmVar) Consortium. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices. Drug-drug interactions and drug/metabolite inhibition must be considered in the case of all metabolizer categories except poor metabolizer. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and patient age.

**Reference Values:**
An interpretive report will be provided.


**Cytochrome P450 2D6 (CYP2D6) Comprehensive Cascade**

**Clinical Information:** The cytochrome P450 (CYP) family of enzymes is a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of the CYP enzymes, CYP2D6, is wholly or partially responsible for the metabolism of many commonly prescribed drugs. The CYP2D6 gene is highly variable with over 100 named alleles. The gene may be deleted, duplicated, and multiplied, and can have multiple sequence variations. In addition, some individuals have genes that are hybrids of CYP2D6 and the CYP2D7 pseudogene. Some individuals have CYP2D6 variants that result in synthesis of an enzyme with decreased or absent catalytic activity. These individuals may process CYP2D6-metabolized medications more slowly. CYP2D6 duplications and multiplications involving active alleles may result in ultrarapid metabolism of CYP2D6-metabolized drugs. CYP2D6 genotype results are used to predict ultrarapid, rapid, normal (extensive), intermediate to normal (extensive), intermediate, poor to intermediate, and poor metabolizer phenotypes.(See Table 1)

**Clinical Information:** The cytochrome P450 (CYP) family of enzymes is a group of oxidative/dealkylating enzymes localized in the microsomes of many tissues including the intestines and liver. One of the CYP enzymes, CYP2D6, is wholly or partially responsible for the metabolism of many commonly prescribed drugs. The CYP2D6 gene is highly variable with over 100 named alleles. The gene may be deleted, duplicated, and multiplied, and can have multiple sequence variations. In addition, some individuals have genes that are hybrids of CYP2D6 and the CYP2D7 pseudogene. Some individuals have CYP2D6 variants that result in synthesis of an enzyme with decreased or absent catalytic activity. These individuals may process CYP2D6-metabolized medications more slowly. CYP2D6 duplications and multiplications involving active alleles may result in ultrarapid metabolism of CYP2D6-metabolized drugs. CYP2D6 genotype results are used to predict ultrarapid, rapid, normal (extensive), intermediate to normal (extensive), intermediate, poor to intermediate, and poor metabolizer phenotypes.(See Table 1)
Table 1. Enzyme Activity of Individual Star Alleles

<table>
<thead>
<tr>
<th>Enzyme Activity</th>
<th>Examples of CYP2D6 star alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (extensive) metabolism</td>
<td>*1, *35</td>
</tr>
<tr>
<td>Intermediate to normal activity</td>
<td>*2A</td>
</tr>
<tr>
<td>Negligible activity</td>
<td>*36</td>
</tr>
</tbody>
</table>

CYP2D6 phenotype is predicted based upon the number of functional, partially functional, and nonfunctional alleles present in a sample. Phenotyping was derived from the Human Cytochrome P450 (CYP) Allele Nomenclature Committee website and the PharmGKB website for the related Clinical Pharmacogenetics Implementation Consortium guidelines. There are instances where a phenotype prediction is not categorical and, in these instances, a range of possible phenotypes will be given. It should be noted that other laboratories may use different phenotype prediction methods as there is no consensus on this at this time. However, the method used here represents the findings of the majority of literature available at this time. Individuals without a detectable gene alteration will have the predicted phenotype of an extensive drug metabolizer and are designated as CYP2D6 *1/*1. Drugs that are metabolized through CYP2D6 may require dosage adjustment based on the individual patient's genotype. Patients who are poor metabolizers may require lower than usual doses to achieve optimal response in the case of drugs that are inactivated by the CYP2D6 enzyme and higher than usual doses in the case of drugs that are activated by CYP2D6 enzyme. Alternatively, patients who are ultrarapid metabolizers may benefit from increased doses in the case of drugs that are inactivated by CYP2D6 enzyme and lower doses in the case of drugs that are activated by CYP2D6. In the absence of clear guidance from FDA on dosing for various metabolizer phenotypes, patients with either ultrarapid or poor metabolism may benefit by switching to comparable alternate medications not primarily metabolized by CYP2D6 or by therapeutic drug monitoring where applicable. Overall, this test provides a comprehensive CYP2D6 genotype result for patients, ensuring a more accurate phenotype prediction. This assay has clinical significance for patients taking or considering medications activated (eg, codeine, tramadol, and tamoxifen) or inactivated (eg, antidepressants and antipsychotics) by the CYP2D6 enzyme. Sequential tier testing associated with this test will be initiated until the least ambiguous phenotype possible is determined.

**Useful For:** Providing information relevant to tamoxifen, codeine, and tramadol, as well as other medications metabolized by CYP2D6 Determining the exact genotype when other methods fail to generate this information or if genotype-phenotype discord is encountered clinically Identifying exact genotyping when required (eg, drug trials, research protocols) Identifying novel variants that may interfere with drug metabolism

**Interpretation:** A comprehensive interpretive report will be provided that combines the results of all tier testing utilized to obtain the final genotype. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Pharmacogene Variation (PharmVar) Consortium.(1) For the CYP2D6 Copy Number Variation assay, the reportable copy number range is 0 to 4 copies for each of the CYP2D6 region assessed. Novel variants will be classified based on known, predicted, or possible effect on gene function and reported with interpretive comments detailing their potential or known significance. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:** A comprehensive interpretive report will be provided.

**Clinical References:**

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 705
**Clinical Information:** CYP3A4 is a member of the CYP3A family of genes located on chromosome 7. The CYP3A subfamily of enzymes is responsible for the metabolism of more than 50% of medications that undergo hepatic metabolism and first-pass metabolism in intestinal epithelial cells, including some lipid-lowering drugs. The CYP3A4 enzyme activity is highly variable. Interindividual differences in enzyme expression may be due to several factors including: variable homeostatic control mechanisms, disease states that alter homeostasis, up- or down-regulation by environmental stimuli, and genetic variation. (1) It should also be noted that most drugs metabolized by CYP3A4 are also metabolized by CYP3A5, but usually to a lesser extent, so testing of CYP3A5 may also be relevant and should be determined on a case by case basis. If CYP3A5 genotyping is needed, order 3A5V / CYP3A5 Genotype. One variant, CYP3A4*22 (c.522-191C>T), has been studied extensively. This variant affects hepatic expression of CYP3A4 and response to statin drugs. The CYP3A4*22 allele is associated with reduced CYP3A4 activity, which may result in a better response to lipid-lowering drugs, such as simvastatin, atorvastatin, or lovastatin. However, reduced CYP3A4 activity may also be associated with statin-induced myopathy, especially for simvastatin. Studies show that in livers with the wild-type genotype (homozygous C or CC) the CYP3A4 mRNA level and enzyme activity were 1.7- and 2.5-fold greater than in heterozygous CYP3A4*22 (CT) and homozygous CYP3A4*22 (TT) carriers, respectively. In 235 patients taking stable doses of drugs for lipid control, carriers of the T allele required significantly lower statin doses for optimal lipid control than did non-T carriers. (2) These results indicate that CYP3A4*22 markedly affects expression of CYP3A4 and could serve as a biomarker for CYP3A4 metabolizer phenotype. The reported allele frequency of CYP3A4*22 is 5% to 8% in Caucasians and 4.3% in African American and Chinese populations. Other alleles have not been as extensively studied in clinical trials but are expected to have similar impacts on statin metabolism and the metabolism of other drugs primarily metabolized by CYP3A4. The following table displays the CYP3A4 variants detected by this assay, the corresponding star allele, and the effect on CYP3A4 enzyme activity. Individuals without a detectable CYP3A4 variant are designated as CYP3A4*1/*1. CYP3A4 Allele cDNA Nucleotide Change Effect on Enzyme Activity *1 None (wild type) Normal activity *8 389G->A No activity *11 1088C->T Reduced activity *12 1117C->T Reduced activity *13 1247C->T No activity *16 554C->G Minimal activity *17 566T->C No activity *18 878T->C Reduced activity *22 522-191C>T Reduced activity *26 802C->T No activity

**Useful For:** Aids in determining therapeutic strategies for drugs that are metabolized by CYP3A4, including atorvastatin, simvastatin, and lovastatin

**Interpretation:** An interpretive report will be provided. The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the Pharmacogene Variation (PharmVar) Consortium. (3) For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomics Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Cytokine Panel

**Interpretation:** Results are used to understand the pathophysiology of immune, infectious, or inflammatory disorders, or may be used for research purposes.

**Reference Values:**
- Tumor Necrosis Factor α (α)
- Interleukin 2
- Interleukin 2 Receptor CD25 Soluble
- Interleukin 12
- Interferon gamma
- Interleukin 4
- Interleukin 5
- Interleukin 10
- Interleukin 13
- Interleukin 17
- Interleukin 1 beta
- Interleukin 6
- Interleukin 8

Cytology FNA (Bill Only)

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

Cytology Touch Prep (Bill Only)

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

Cytology Touch Prep Additional (Bill Only)

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

Cytomegalovirus (CMV) Antibodies, IgG, Serum

**Clinical Information:** Cytomegalovirus (CMV) is a member of the Herpesviridae family of viruses and usually causes asymptomatic infection after which it remains latent in patients, primarily within bone marrow derived cells.(1) Primary CMV infection in immunocompetent individuals may also manifest as a mononucleosis-type syndrome, similar to primary Epstein-Barr virus infection, with fever,
malaise, and lymphadenopathy. CMV is a significant cause of morbidity and mortality among bone marrow or solid organ transplant recipients, individuals with AIDS and other immunosuppressed patients due to virus reactivation or from a newly acquired infection. Infection in these patient populations can affect almost any organ and lead to multiorgan failure. CMV is also responsible for congenital disease among newborns and is one of the TORCH infections (toxoplasmosis, other infections including syphilis, rubella, CMV, and herpes simplex virus). CMV seroprevalence increases with age. In the United States the prevalence of CMV specific antibodies increases from approximately 36% to over 91% in adolescents between the ages of 6 to 11 and adults over 80 years old, respectively.

**Useful For:** Determining whether a patient (especially transplant recipients, organ and blood donors) has had a recent infection or previous exposure to cytomegalovirus

**Interpretation:** Positive cytomegalovirus (CMV) IgG results indicate past or recent CMV infection. These individuals may transmit CMV to susceptible individuals through blood and tissue products. Equivocal CMV IgG results may occur during acute infection or may be due to nonspecific binding reactions. Submit an additional sample for testing if clinically indicated. Individuals with negative CMV IgG results are presumed to not have had prior exposure or infection with CMV and are, therefore, considered susceptible to primary infection.

**Reference Values:**
Negative (reported as positive, negative, or equivocal)

**Clinical References:**
Cytomegalovirus (CMV) Antibodies, IgM, Serum

Clinical Information: Cytomegalovirus (CMV) is a member of the Herpesviridae family of viruses and usually causes asymptomatic infection after which it remains latent in patients, primarily within bone marrow derived cells. Primary CMV infection in immunocompetent individuals may also manifest as a mononucleosis-type syndrome, similar to primary Epstein-Barr virus infection, with fever, malaise, and lymphadenopathy. CMV is a significant cause of morbidity and mortality among bone marrow or solid organ transplant recipients, individuals with AIDS and other immunosuppressed patients due to virus reactivation or from a newly acquired infection. Infection in these patient populations can affect almost any organ and lead to multiorgan failure. CMV is also responsible for congenital disease among newborns and is 1 of the TORCH infections (toxoplasmosis, other infections including syphilis, rubella, CMV, and herpes simplex virus). CMV seroprevalence increases with age. In the United States the prevalence of CMV specific antibodies increases from approximately 36% to over 91% in adolescents between the ages of 6 to 11 and adults over 80 years old, respectively.

Useful For: Aiding in the diagnosis of acute infection with cytomegalovirus (CMV)

Interpretation: A negative cytomegalovirus (CMV) IgM result suggests that the patient is not experiencing acute or active infection. However, a negative result does not rule-out primary CMV infection. It has been reported that CMV-specific IgM antibodies were not detectable in 10% to 30% of cord blood sera from infants demonstrating infection in the first week of life. In addition, up to 23% (3/13) of pregnant women with primary CMV infection did not demonstrate detectable CMV IgM responses within 8 weeks postinfection. In cases of primary infection where the time of seroconversion is not well defined as high as 28% (10/36) of pregnant women did not demonstrate CMV-IgM antibody. Positive CMV IgM results indicate a recent infection (primary, reactivation, or reinfection). IgM antibody responses in secondary (reactivation) CMV infections have been demonstrated in some CMV mononucleosis patients, in a few pregnant women, and in renal and cardiac transplant patients. Levels of antibody may be lower in transplant patients with secondary, rather than primary, infections. Equivocal CMV IgM results may occur during acute infection or may be due to nonspecific binding reactions. Submit an additional sample for testing if clinically indicated.

Reference Values:
CMV IgM: Negative
CMV IgG: Negative

Reference values apply to all ages.

Reference values apply to all ages.

**Clinical References:**

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**CMVC8 88826**

**Cytomegalovirus (CMV) CD8 T-Cell Immune Competence, Quantitative Assessment by Flow Cytometry**

**Clinical Information:**
Cytomegalovirus (CMV), a double-stranded DNA virus, belongs to the Herpesviridae family of viruses and is structurally similar to other herpes viruses. Although many human strains of CMV exist, there is little genetic homology between human CMV and CMV of other species. The reported seroprevalence rates of CMV range from 40% to 100% in the general population. In the urban United States, the seroprevalence of CMV has been reported to be 60% to 70%.(1) However, data from Mayo Clinic's laboratory indicate that the seroprevalence in the Midwestern US population is closer to 30% (unpublished observations). Once CMV infection occurs, the virus spreads hematogenously to almost every organ. After acute infection, the virus enters a latent phase. Activation from this phase can be seen after acute illness, immunosuppression in allogeneic hematopoietic stem cell transplantation (HSCT) or solid organ transplantation, or use of chemotherapy agents. CMV infection or reactivation has been implicated in allograft rejection in renal(2) and cardiac transplantation.(1) In cardiac transplants, CMV infection has been shown to contribute to accelerated development of transplant atherosclerosis (cardiac allograft vasculopathy). CMV remains a significant cause of morbidity and mortality after HSCT. Of allogeneic HSCT patients who are CMV-seropositive, 60% to 70% will experience reactivation and, without ganciclovir or other preemptive therapy, 20% to 30% will develop end-organ disease.(3) CD8 T cells play a critical role in viral immunity, and CD8 T-cell effector functions include cytotoxicity and cytokine production. Cytotoxicity occurs after CD8 T-cell activation, causing target cell apoptosis. Cytotoxic T-cell responses mediate killing of target cells via 2 major pathways, granule-dependent (perforin and granzymes) and granule-independent (Fas and Fas ligand [FasL]) mechanisms. The granule-dependent pathway does not require the de novo synthesis of proteins by effector CD8 T cells, but rather it utilizes preformed lytic granules located within the cytoplasm. Among the proteins in these preformed lytic granules are the lysosomal-associated membrane proteins (LAMP), including LAMP-1 (CD107a) and LAMP-2 (CD107b). These proteins are not normally found on the surface of T cells. Degranulation of activated CD8 T cells occurs rapidly after T-cell receptor (TCR) stimulation, exposing CD107a and CD107b. The cytokines produced by activated T cells include interferon-gamma (IFN-gamma), tumor necrosis factor alpha (TNF-alpha), macrophage inflammatory protein 1 alpha (MIP-1 alpha), macrophage inflammatory protein 1 beta (MIP-1 beta), and interleukin-2 (IL-2). Several studies have shown the importance of cytotoxic T-cell responses to CMV in conferring protection from subsequent CMV disease. Antiviral drugs have helped reduce the incidence of early CMV infection, and acyclovir and ganciclovir have been the mainstay of antiviral treatment for a number of years, although these drugs have poor bioavailability.(4) The development of the new antiviral drugs valacyclovir and valganciclovir (by the addition of a valine ester) has increased the bioavailability of these drugs by 10-fold.(4) There is some data to suggest valganciclovir prophylaxis may be considered for HSCT patients who are at high risk for infection and disease, though there is a need for further study in this area.(5) Two main strategies have been used for the prevention of early CMV infection and disease in CMV-seropositive patients and in seronegative recipients who receive a seropositive graft-preemptive therapy: - Patient monitoring for CMV infection and treatment only when CMV viremia is present. - Prophylactic management-where all patients receive treatment after transplantation with the goal of preventing CMV disease.(5) The disadvantage of prophylactic therapy is that it requires monitoring for myelosuppression and infections-side effects of antiviral drug therapy. Despite this disadvantage, there are several reasons to consider prophylaxis, including the fact that the incidence of recurrent infections after treatment is 30% to 40%.(5) Patients receiving preemptive therapy have a 5% CMV disease break-through, and prophylaxis reduces the risk of viral reactivation. Late CMV infection occurs 3
months after transplantation and is now recognized as a significant cause of morbidity after allogeneic HSCT. These complications usually occur in the setting of continued immunosuppression for chronic graft-versus-host disease (GVHD). The clinical manifestations of late CMV disease differ slightly from those seen early after transplantation. Within the first 100 days after HSCT, almost all patients with CMV disease have CMV pneumonia or gastrointestinal disease. In late CMV disease, the more unusual manifestations of CMV infection (eg, CMV retinitis, CMV-associated bone marrow failure, or CMV encephalitis) tend to occur.(6) These late manifestations occur in a setting of continued CMV-specific T-cell immunodeficiency. Therefore, it is necessary to monitor CMV-specific CD8 T-cell responses, in addition to viral load, to effectively identify patients at higher risk of CMV disease. It has been shown that ganciclovir may delay the recovery of the protective CMV-specific T-cell response, which may contribute to the occurrence of late CMV disease.(7) The use of ganciclovir as early treatment after detection of CMV in blood or other body fluid and as a prophylaxis for CMV infection in bone marrow transplant (BMT) and heart transplant recipients has dramatically reduced the incidence of CMV in these immunocompromised hosts. Yet, early treatment and prophylaxis have not been uniformly successful, with up to 15% of BMT recipients developing CMV disease after discontinuation of antiviral therapy. Similarly, patients undergoing lung transplantation have been shown to be only transiently protected with antiviral agents. These data suggest that the CMV-specific responses necessary for protection may not recover during the time the host is receiving antiviral therapy. Ganciclovir exerts its antiviral effects at the stage of viral DNA replication and, therefore, in the presence of the drug, infected cells may express some of the immediate early and early gene products, but not the full complement of CMV genes required for replication and virion formation. In latently infected CMV-seropositive individuals, the HLA class I-restricted cytotoxic T lymphocyte response to CMV is predominantly specific for epitopes derived from structural virion proteins. Therefore, in patients receiving ganciclovir, the viral antigens may be inadequate to activate host T-cell responses, resulting in the failure to reconstitute CMV-specific immunity. In fact, a prospective, randomized placebo-controlled study of ganciclovir prophylaxis revealed that when ganciclovir therapy is discontinued, a larger fraction of patients (who received the drug) are deficient in CMV-specific T-cell immunity at day 100 than in the placebo group.(7) That study also showed that bone marrow donor serology has an important influence on the early detection of virus-specific T-cell responses.(7) Not all medical centers use ganciclovir for prophylaxis; some use acyclovir and the same findings may apply in this case as well. In a more recent study, it was shown that impaired CD8 function was associated with the use of high-dose steroids, bone marrow as a source of stem cells, and CD8 T-cell lymphopenia.(3) In the absence of high-dose steroids, low-level subclinical CMV antigenemia was found to stimulate both CD4 and CD8 functional recovery in recipients of ganciclovir prophylaxis, suggesting that subclinical CMV reactivation while on antiviral therapy can be a potent stimulator of T-cell function.(3) Regardless of antiviral therapy, immunologic reconstitution remains the key element in protection from late-onset CMV disease. This test assesses the number of CMV-specific CD8 T cells and their function (activation via production of the cytokine IFN-gamma and cytotoxic potential via CD107a and CD107b as markers of degranulation) using a panel of 5 major histocompatibility complex (MHC) class I alleles (HLA A1, A2, B7, B8, and B35) along with their respective immunodominant CMV epitopes. This 3-part assay allows a comprehensive assessment of CMV-specific CD8 T cell immunity and, when combined with evaluation of viremia using molecular analyses, provides a more accurate picture of the nature of CMV reactivation and the corresponding immune response than evaluating viremia alone. Assessment of Global CD8 T-Cell Function: CD8 T cell activation occurs either through the TCR-peptide-MHC or by use of a mitogen (eg, phorbol myristate acetate and the calcium ionophore ionomycin). Mitogen-mediated activation is antigen nonspecific. Impairment of global CD8 T cell activation (due to inherent cellular immunodeficiency or as a consequence over immunosuppression by therapeutic agents) results in reduced production of IFN-gamma and other cytokines, reduced cytotoxic function, and increased risk for developing infectious complications. Agents associated with over-immunosuppression include the calcineurin inhibitors (eg, cyclosporine A, FK506 [Prograf/tacrolimus], and rapamycin [sirolimus]), antimetabolites (eg, mycophenolate mofetil), and thymoglobulin. The incorporation of global CD8 T cell function in this assay is helpful in determining if the lack of CMV-specific (antigen-specific) response is due to a global impairment in CD8 T cell function, due to immunosuppression or other causes, or whether the lack of CMV CD8 T cell immunity is unrelated to overall CD8 T cell function. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon, with no change between noon and afternoon. Natural killer
cell counts, on the other hand, are constant throughout the day.(8) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(9-11) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naïve versus effector CD4 and CD8 T cells.(9) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening (12), and during summer compared to winter.(13) These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

**Useful For:** Assessing cytomegalovirus (CMV)-specific immune competence in allo-hematopoietic stem cell transplantation patients who are at risk for developing late CMV disease (beyond day 100 after transplant) Assessing CMV-specific immune competence in solid organ transplant patients who are at high risk for CMV reactivation posttransplant Monitoring immune competence in patients post-primary CMV infection after transplant who are at risk for CMV reactivation after the cessation of antiviral prophylaxis Identifying individuals who are likely to be protected from posttransplant CMV infection and those who are at higher risk of CMV reactivation The global CD8 T cell immune competence assay is useful for determining over immunosuppression within the CD8 T cell compartment, when used on transplant recipients and patients with autoimmune disorders receiving therapy with immunosuppressant agents

**Interpretation:** For allogeneic hematopoietic stem cell transplantation (HSCT) and solid organ transplant patients who are cytomegalovirus (CMV)-seropositive and at risk for CMV reactivation, posttransplant results should be compared to pretransplant (preconditioning/baseline) results. The report includes absolute CD3 and CD8 T-cell counts as well as a derived CMV-specific CD8 T-cell count (derived from CD3 and CD8 T-cell counts). The absolute count of CMV-CD8 T cells that are activated and have cytotoxic function in response to specific CMV peptide is also provided. The data from the 3 components of this assay should be interpreted together and not individually. In the setting of CMV viremia, frequent monitoring of CMV-immune competence helps define the evolution of the CMV-immune response. In this clinical context, CMV-immune competence should be measured as frequently as viral load to determine correlation between the 2 parameters. CMV-specific CD8 T-cell counts may show a decline in numbers over time in the absence of active infection or antigenemia. The absence of CMV-specific CD8 T cells may be a risk factor in the immune-compromised or immune-incompetent transplant patient, who is at risk for CMV reactivation. The presence of CMV-specific CD8 T cells may not be protective in itself. If the CMV-specific CD8 T cells do not show appropriate cytotoxic function (due to the fact that they recognize CMV epitopes that do not effectively induce a cytotoxic response), these patients may be at higher risk of an inadequate immune response to CMV infection. While the reference values provide a guideline of CMV-specific CD8 T-cell numbers and function in a cohort of healthy individuals, baseline (pretransplant/preconditioning) assessments should be taken into consideration when determining CMV-specific immune competence posttransplant. Correlation between data from multiple post-transplant specimens (if available) and the presence or absence of viremia (or active CMV disease) also are useful in the interpretation of results. CD8 T cell counts are elevated when the immune system is initially reconstituted post-HSCT, and the CD4 to CD8 ratio can be inverted for about 12 months post-HSCT. Interferon-gamma (IFN-gamma) and CD107a/b expression below the defined reference range are consistent with a global impairment in CD8 T cell function, most likely due to over-immunosuppression. IFN-gamma and CD107a/b levels greater than the defined reference range are unlikely to have any clinical significance.

**Reference Values:**
- Total CD3 T cells: 884-5,830 x 10(3)/mL
- Total CD8 T cells: 168-1,847 x 10(3)/mL
- Total CMV CD8 T cells: 0-115 x 10(3)/mL

The adult reference values were determined for healthy adult controls ages 20 to 80 years (n=94), for HLA A1, A2, B7, B8, and B35 alleles.

Reference values for CMV-specific T cells that are functional (interferon-gamma+, IFN-g+) and have cytotoxic activity (CD107a and CD107b expression, CD107 a/b+):
- Total CMV CD8 T-cells IFN-g: 0.028-52.200 x 10(3)/mL
- Total CMV CD8 T-cells CD107a/b: 0.252-50.760 x 10(3)/mL
The 95% confidence interval reference values were determined from 102 healthy adult donors:

Interferon-gamma (IFN-gamma) expression (as % CD8 T cells): 10.3-56.0%
CD107a/b expression (as % CD8 T cells): 8.5-49.1%

The reference values were developed for each of the following 4 major histocompatibility complex class I alleles: A1, A2, B7, and B8 (n=45). We were unable to develop ranges for the B35 allele due to a lack of matching donors. The data is expressed as the absolute number of CMV-specific CD8 T cells that are IFN-gamma+ or CD107a/b+.

**Clinical References:**

**CMVQN 601954**

**Cytomegalovirus (CMV) DNA Detection and Quantification by Real-Time PCR, Plasma**

**Clinical Information:** Cytomegalovirus (CMV) is a common and major cause of opportunistic infection in organ transplant recipients, causing significant morbidity and mortality. CMV infection and disease typically occur during the first year after organ transplantation after cessation of antiviral prophylaxis. Such infection usually manifests as fever, leukopenia, hepatitis, colitis, or retinitis. Other manifestations of CMV infection in this population may be more subtle and include allograft injury and loss, increased susceptibility to infections with other organisms, and decreased patient survival (ie, indirect effects). The risk of CMV disease is highest among organ recipients who are CMV seronegative prior to transplantation and receive allografts from CMV-seropositive donors (ie, CMV D+/R-mismatch). The infection is transmitted via latent CMV present in the transplanted organ donor and the virus subsequently reactivates, causing a primary CMV infection in the recipient. CMV disease may also occur from reactivation of the virus already present within the recipients. Factors, such as the type of organ transplanted, intensity of the antirejection immunosuppressive therapy, advanced age, and presence of comorbidities in the recipient, are also associated with increased risk for CMV disease after allograft transplantation. Lung, heart, small intestine, pancreas, and kidney-pancreas transplant recipients are at greater risk for CMV infection than kidney and liver transplant recipients. Among the various clinical laboratory diagnostic tests currently available to detect CMV infection, nucleic acid amplification tests (eg, PCR) are the most sensitive and specific detection methods. In addition, quantification of CMV DNA level in peripheral blood (ie, CMV viral load) is used routinely to determine when to initiate preemptive antiviral therapy, diagnose active CMV disease, and monitor response to antiviral therapy. A number of factors can affect CMV viral load results, including the...
specimen type (whole blood versus plasma), biologic properties of CMV, performance characteristics of the quantitative assay (eg, limit of detection, limits of quantification, linearity, and reproducibility), degree of immunosuppression, and intensity of antiviral therapy. In general, higher CMV viral loads are associated with tissue-invasive disease, while lower levels are associated with asymptomatic infection. However, the viral load in the peripheral blood compartment may be low or undetectable in some cases of tissue-invasive disease. Since a wide degree of overlap exists in CMV viral load and disease, a rise in viral load over time is more important in predicting CMV disease than a single viral load result at a given time point. Therefore, serial monitoring (eg, weekly intervals) of organ transplant recipients with quantitative CMV PCR is recommended in such patients at risk for CMV disease. Since changes in viral load may be delayed by several days in response to antiviral therapy and immunosuppression, viral load should not be monitored more frequently than a weekly basis. Typically, CMV viral load changes of greater than 0.5 log IU/mL are considered biologically significant changes in viral replication. Patients with suppression of CMV replication (ie, viral load of <35 or <1.54 log IU/mL at days 7, 14, and 21 of treatment) had shorter times to resolution of clinical disease than those without viral suppression. No degree of relative viral load reduction from pretreatment level was associated with faster resolution of CMV disease.

**Useful For:** Detection and quantification of cytomegalovirus (CMV) viremia Monitoring CMV disease progression and response to antiviral therapy

**Interpretation:** The quantification range of this assay is 35 to 10,000,000 IU/mL (1.54 log to 7.00 log IU/mL), with a 95% or higher limit of detection at 35 IU/mL. A result of “Undetected” indicates the absence of cytomegalovirus (CMV) DNA in the plasma (see Cautions below). A result of “<35 IU/mL (<1.54 log IU/mL)” indicates that CMV DNA is detected in the plasma, but the assay cannot accurately quantify the CMV DNA present below this level. A quantitative value (reported in IU/mL and log IU/mL) indicates the level of CMV DNA (ie, viral load) present in the plasma. A result of “>10,000,000 IU/mL (>7.00 log IU/mL)” indicates that CMV DNA level present in plasma is above 10,000,000 IU/mL (7.00 log IU/mL), and the assay cannot accurately quantify CMV DNA present above this level.

**Reference Values:**

Undetected

**Clinical References:**

**FCYTO** 58006

**Cytomegalovirus (CMV) Genotypic Drug Resistance**

**Clinical Information:** Treatment of CMV diseases includes three licensed drugs: ganciclovir, foscarnet and cidofovir. All three drugs inhibit the viral DNA polymerase through various mechanisms. Over time, as CMV makes copies of itself, the virus can change its structure. These changes may make CMV resistant to the effects of antiviral drugs. Therefore, it is important to detect resistance as quickly and accurately as possible for proper management of CMV infection.

**Reference Values:**

Not Detected

**FCMIG** 75226

**Cytomegalovirus (CMV) IgG Avidity (AviDx), ELISA**

**Clinical Information:** Discrimination between recent (primary) and past cytomegalovirus (CMV) infection can be an important tool in the clinical management of transplant recipients and pregnant women. Although nearly all individuals with recent CMV infection are positive for CMV IgM, individuals with past CMV may also express CMV IgM following viral reactivation; thus, detection of
CMV IgM is not a reliable indicator of recent CMV infection. Measurement of CMV IgG avidity can assist in discriminating recent from past CMV infection. Although a low avidity index is a reliable indicator of CMV infection within the previous 6 months, a high avidity index is more meaningful from a clinical standpoint; a high avidity index essentially excludes the possibility that infection occurred within the previous 4 months. Avidity index values should be considered within the context of other laboratory findings and clinical signs.

**Interpretation:**
- < or = 0.50 Low Avidity Index
- 0.51 – 0.59 Intermediate Avidity Index
- > or = 0.60 High Avidity Index

**Reference Values:**
- > or = 0.60

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**CMVI 70406**

**Cytomegalovirus (CMV) Immunostain, Technical Component Only**

**Clinical Information:** Cytomegalovirus (CMV) stain visualizes the intranuclear and cytoplasmic viral inclusions of CMV-infected cells. CMV can cause severe systemic infection (primary or reactivated infection) in immunocompromised hosts. Antibodies to cytomegalovirus fail to react with any normal human tissue.

**Useful For:** Aids in the identification of cytomegalovirus infection

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**LCMV 81240**

**Cytomegalovirus (CMV), Molecular Detection, PCR**

**Clinical Information:** Infection with cytomegalovirus (CMV) is a significant cause of morbidity and mortality in transplant recipients and other immunocompromised hosts. Specific neurologic syndromes associated with CMV infection include subacute radiculomyelopathy, peripheral neuropathy, and encephalitis. CMV-associated central nervous system (CNS) disease occurs most commonly in immunocompromised patients. Histologic evidence of CMV infections in autopsy brain tissue was identified in 20% to 40% of AIDS patients. In 2 separate studies, CMV (DNA) was the most common herpesvirus (29/181, 16/49) detected from cerebrospinal fluid of patients with AIDS. CNS infections with CMV can also occur in immunocompetent patients. CMV is a leading cause of congenital viral infections worldwide, and laboratory testing by real-time PCR is useful in the diagnosis of neonatal CMV disease.

**Useful For:** Rapid qualitative detection of cytomegalovirus (CMV) DNA

This test is not intended for
the monitoring of cytomegalovirus (CMV) disease progression.

**Interpretation:** Detection of cytomegalovirus (CMV) DNA in a specimen supports the clinical diagnosis of infection due to this virus. Studies indicate that CMV DNA is not detected by PCR in cerebrospinal fluid from patients without central nervous system disease caused by this virus.

**Reference Values:**
Negative

**Clinical References:**

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**ANCA**

**9441**

**Cytoplasmic Neutrophil Antibodies, Serum**

**Clinical Information:** Antineutrophil cytoplasmic antibodies (ANCA) can occur in patients with autoimmune vasculitis including Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), or organ-limited variants thereof such as pauci-immune necrotizing glomerulonephritis.(1) Detection of ANCA is a well-established diagnostic test for the evaluation of patients suspected of having autoimmune vasculitis. ANCA react with enzymes in the cytoplasmic granules of human neutrophils including proteinase 3 (PR3), myeloperoxidase (MPO), elastase, and cathepsin G. Antibodies to PR3 occur in patients with WG (both classical WG and WG with limited end-organ involvement) and produce a characteristic pattern of granular cytoplasmic fluorescence on ethanol-fixed neutrophils called the cANCA pattern. Antibodies to MPO occur predominately in patients with MPA and produce a pattern of perinuclear cytoplasmic fluorescence on ethanol-fixed neutrophils called the pANCA pattern.

**Useful For:** Antineutrophil cytoplasmic antibodies (cANCA and pANCA): -Evaluating patients suspected of having autoimmune vasculitis (both Wegener granulomatosis [WG] and microscopic polyangiitis) cANCA titer: -May be useful for monitoring treatment response in patients with WG (systemic or organ-limited disease); increasing titer suggests relapse of disease, while a decreasing titer suggests successful treatment When used for diagnosis it is recommended that specific tests for proteinase 3 (PR3) ANCA and myeloperoxidase (MPO) ANCA be performed in addition to testing for cANCA and pANCA.(2) This panel of tests is available by ordering the VASC / Antineutrophil Cytoplasmic Antibodies Vasculitis Panel, Serum.

**Interpretation:** Positive results for antineutrophil cytoplasmic antibodies (cANCA or pANCA) are consistent with the diagnosis of Wegener granulomatosis (WG), either systemic WG with respiratory and renal involvement or limited WG with more restricted end-organ involvement. Positive results for pANCA are consistent with the diagnosis of autoimmune vasculitis including microscopic polyangiitis (MPA) or pauci-immune necrotizing glomerulonephritis. Sequential measurements of titers of cANCA may be useful to indicate the clinical course of patients with WG. Changes in titer of > or =2 serial dilutions are considered significant.(3) In patients with very low levels of cANCA, the immunofluorescent staining pattern may mimic the pANCA pattern. In patients with MPA, monitoring of disease activity may be performed by measuring MPO ANCA (MPO / Myeloperoxidase Antibodies, IgG, Serum).

**Reference Values:**
Negative
If positive for cANCA, results are titered.

**Clinical References:**

### D-Dimer, Plasma

**Clinical Information:** Thrombin, the terminal enzyme of the plasma procoagulant cascade, cleaves fibrinopeptides A and B from fibrinogen, generating fibrin monomer. Fibrin monomer contains D domains on each end of the molecule and a central E domain. Most of the fibrin monomers polymerize to form insoluble fibrin, or the fibrin clot, by repetitive end-to-end alignment of the D domains of 2 adjacent molecules in lateral contact with the E domain of a third molecule. The fibrin clot is subsequently stabilized by thrombin-activated factor XIII, which covalently cross-links fibrin monomers by transamidation, including dimerization of the D domains of adjacent polymerized fibrin monomers. The fibrin clot promotes activation of fibrinolysis by catalyzing the activation of plasminogen (by plasminogen activators) to form plasmin enzyme. Plasmin proteolytically degrades cross-linked fibrin, ultimately producing soluble fibrin degradation products of various sizes that include cross-linked fragments containing neoantigenic D-dimer (DD) epitopes. Plasmin also degrades fibrinogen to form fragments X, Y, D, and E. D-dimer immunoassays use monoclonal antibodies to DD neoantigen and mainly detect cross-linked fibrin degradation products, whereas the fibrinogenolytic degradation products-X, Y, D, and E, and their polymers may be derived from fibrinogen or fibrin.

Therefore, the blood content of D-dimer indirectly reflects the generation of thrombin and plasmin, roughly indicating the turnover or activation state of the coupled blood procoagulant and fibrinolytic mechanisms.(1)

**Useful For:** Diagnosis of intravascular coagulation and fibrinolysis (ICF), also known as disseminated intravascular coagulation (DIC), especially when combined with clinical information and other laboratory test data (eg, platelet count, assays of clottable fibrinogen and soluble fibrin monomer complex, and clotting time assays-prothrombin time and activated partial thromboplastin time)

Excluding the diagnosis of acute pulmonary embolism or deep vein thrombosis, particularly when results of a sensitive D-dimer assay are combined with clinical information, including pretest disease probability.

**Interpretation:** D-dimer values < or =250 ng/mL DDU (< or =0.50 mcg/mL FEU) are normal. Within the reportable normal range (110-250 ng/mL DDU; 0.22-0.50 mcg/mL FEU), measured values may reflect the activation state of the procoagulant and fibrinolytic systems, but the clinical utility of such quantitation is not established. A normal D-dimer result (< or =250 ng/mL DDU; < or =0.50 mcg/mL FEU) has a negative predictive value of approximately 95% for the exclusion of acute pulmonary embolism (PE) or deep vein thrombosis when there is low or moderate pretest PE probability. Increased D-dimer values are abnormal but do not indicate a specific disease state. D-dimer values may be increased as a result of: -Clinical or subclinical disseminated intravascular coagulopathy (DIC)/intravascular coagulation and fibrinolysis (ICF). -Other conditions associated with increased activation of the procoagulant and fibrinolytic mechanisms such as recent surgery, active or recent bleeding, hematomas, trauma, or thromboembolism. -Association with pregnancy, liver disease, inflammation, malignancy or hypercoagulable (procoagulant) states. The degree of D-dimer increase does not definitely correlate with the clinical severity of associated disease states.

**Reference Values:**
Only orderable as part of a coagulation consultation. For more information see 1 of the following:
BDIAC / Bleeding Diathesis Profile, Comprehensive
DCICF / DIC/ICF Profile

< or =250 ng/ml D-Dimer Units (DDU)
< or =0.5 mcg/mL Fibrinogen Equivalent Units (FEU)

D-Dimer, Plasma

Clinical Information: The specific degradation of fibrin (ie, fibrinolysis) is the reactive mechanism responding to the formation of fibrin. Plasmin is the fibrinolytic enzyme derived from inactive plasminogen. Plasminogen is converted into plasmin by plasminogen activators. The main plasminogen activators are tissue plasminogen activator (tPA) and pro-urokinase, which is activated into urokinase (UK) by, among others, the contact system of coagulation. In the bloodstream, plasmin is rapidly and specifically neutralized by alpha 2-antiplasmin, thereby restricting its fibrinogenolytic activity and localizes the fibrinolysis on the fibrin clot. On the fibrin clot, plasmin degrades fibrin into various products (ie, D-dimers). Antibodies specific for these products, which do not recognize fibrinogen, have been developed. The presence of these various fibrin degradation products, among which D-dimer is the terminal product, is the proof that the fibrinolytic system is in action in response to coagulation activation. Elevated D-dimer levels are found in association with disseminated intravascular coagulation (DIC), pulmonary embolism (PE), deep vein thrombosis (DVT), trauma, and bleeding. D-dimer may also be increased in association with pregnancy, liver disease, malignancy, inflammation, or a chronic hypercoagulable state.

Useful For: Excluding the diagnosis of acute pulmonary embolism or deep vein thrombosis, particularly when results of a sensitive D-dimer assay are combined with clinical information, including pretest disease probability(1-4) Diagnosis of intravascular coagulation and fibrinolysis, also known as disseminated intravascular coagulation, especially when combined with clinical information and other laboratory test data (eg, platelet count, assays of clottable fibrinogen and soluble fibrin monomer complex, and clotting time assays-prothrombin time and activated partial thromboplastin time)(5)

Interpretation: A normal D-dimer result less than or equal to 500 ng/mL fibrinogen equivalent units (FEU) on the IL D-Dimer HS500 kit has a negative predictive value of approximately 100% (range 97%-100%) and is FDA approved for the exclusion of acute pulmonary embolism (PE) and deep vein thrombosis (DVT) when there is low or moderate pretest probability for PE or DVT. D-dimer concentrations increase with age and, thus, the specificity for DVT and PE exclusion decreases with age. For DVT or PE exclusion, in addition to clinical pretest probability, age-adjusted D-dimer cutoffs are suggested for patients more than 50 years of age. Recent evidence suggests using clinical pretest probability and age-adjusted cutoffs to improve the performance of D-dimer testing in patients greater than 50 years of age. In recent studies, when compared to a fixed D-dimer cutoff, age adjusted D-dimer cutoff values (calculated as follows: age [years] x 10 ng/mL) resulted in equivalent outcomes and no additional false negative findings.(7-8) Increased D-dimer values are abnormal but do not indicate a specific disease state. D-dimer values may be increased as a result of: -Clinical or subclinical disseminated intravascular coagulation/intravascular coagulation and fibrinolysis -Other conditions associated with increased activation of the procoagulant and fibrinolytic mechanisms such as recent surgery, active or recent bleeding, hematomas, trauma, or thromboembolism -Association with pregnancy, liver disease, inflammation, malignancy, or hypercoagulable (procoagulant) states The degree of D-dimer increase does not definitively correlate with the clinical severity of associated disease states.

Reference Values:
< or =500 ng/mL Fibrinogen Equivalent Units (FEU)
D-dimer values < or =500 ng/mL FEU may be used in conjunction with clinical pretest probability to exclude deep vein thrombosis (DVT) and pulmonary embolism (PE).

**Clinical References:**

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**DLAC 8878**

**D-Lactate, Plasma**

**Clinical Information:** D-lactate is produced by bacteria residing in the colon when carbohydrates are not completely absorbed in the small intestine. When large amounts of D-lactate are present, individuals can experience metabolic acidosis, altered mental status (from drowsiness to coma), and a variety of other neurologic symptoms, particularly dysarthria and ataxia. D-lactic acidosis is typically observed in patients with a malabsorptive disorder, such as short-bowel syndrome, or, following a jejunoileal bypass. In addition, healthy children presenting with gastroenteritis may also develop the critical presentation of D-lactic acidosis. Routine lactic acid determinations in blood will not reveal abnormalities because most lactic acid assays measure only L-lactate. Accordingly, D-lactate analysis must be specifically requested (eg, DLAC / D-Lactate, Plasma). However, as D-lactate is readily excreted in urine, DLAU / D-Lactate, Urine is the preferred specimen for D-lactate determinations.

**Useful For:** An adjunct to urine D-lactate (preferred), in the diagnosis of D-lactic acidosis

**Interpretation:** Increased levels are consistent with D-lactic acidosis. However, because D-lactate is readily excreted, urine determinations are preferred.

**Reference Values:**

0.0-0.25 mmol/L

**Clinical References:**

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**DLAU 8873**

**D-Lactate, Urine**

**Clinical Information:** D-lactate is produced by bacteria residing in the colon when carbohydrates are not completely absorbed in the small intestine. When large amounts are absorbed it can cause metabolic acidosis, altered mental status (from drowsiness to coma), and a variety of other neurologic symptoms, in particular dysarthria and ataxia. Although a temporal relationship has been described between elevations of plasma and urine D-lactate and the accompanying encephalopathy, the mechanism of neurologic manifestations has not been elucidated. D-lactic acidosis is typically observed in patients with short-bowel syndrome and following jejunoileal bypass resulting in carbohydrate malabsorption. In addition, healthy children presenting with gastroenteritis may also develop the critical presentation of D-lactic acidosis. Routine lactic acid determinations in blood will not reveal abnormalities because most lactic acid assays measure only L-lactate. Accordingly, D-lactate analysis
must be specifically requested (eg, DLAC / D-Lactate, Plasma). However, as D-lactate is readily excreted in urine, this is the preferred specimen for D-lactate determinations.

**Useful For:** Preferred test for diagnosing D-lactate acidosis, especially in patients with jejunoileal bypass and short-bowel syndrome

**Interpretation:** Increased levels are diagnostic.

**Reference Values:**
0.0-0.25 mmol/L

**Clinical References:**

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**Dairy and Grain Allergen Profile**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens responsible for anaphylaxis, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or ≥100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Clinical References:**
**Dandelion, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


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**Dantrolene, Serum/Plasma**

**Reference Values:** Reporting limit determined each analysis

**Synonym(s):** Dantrium

Usual therapeutic range: 0.2 - 3.5 mcg/mL
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<th>Interpretation</th>
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<td>Negative</td>
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<tr>
<td>1</td>
<td>0.35-0.69</td>
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<td>2</td>
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Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
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<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
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</table>

Reference values apply to all ages.


Deer Epithelium, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**DHEA_81405**

**Dehydroepiandrosterone (DHEA), Serum**

**Clinical Information:** Dehydroepiandrosterone (DHEA) is the principal human C-19 steroid. DHEA has very low androgenic potency, but serves as the major direct or indirect precursor for most sex steroids. DHEA is secreted by the adrenal gland and production is at least partly controlled by adrenocorticotropic hormone (ACTH). The bulk of DHEA is secreted as a 3-sulfoconjugate dehydroepiandrosterone sulfate (DHEAS). Both hormones are albumin bound, but DHEAS binding is much tighter. As a result, circulating concentrations of DHEAS are much higher (>100-fold) compared to DHEA. In most clinical situations, DHEA and DHEAS results can be used interchangeably. In gonads and several other tissues, most notably skin, steroid sulfatases can convert DHEAS back to DHEA, which can then be metabolized to stronger androgens and to estrogens. During pregnancy, DHEA/DHEAS and their 16-hydroxylated metabolites are secreted by the fetal adrenal gland in large quantities. They serve as precursors for placental production of the dominant pregnancy estrogen, estriol. Within weeks after birth, DHEA/DHEAS levels fall by 80% or more and remain low until the onset of adrenarche at age 7 or 8 in girls and age 8 or 9 in boys. Adrenarche is a poorly understood phenomenon, peculiar to higher primates, that is characterized by a gradual rise in adrenal androgen production. It precedes puberty, but is not casually linked to it. Early adrenarche is not associated with early puberty or with any reduction in final height or overt androgenization. However, girls with early adrenarche may be at increased risk of polycystic ovarian syndrome as adults and some boys may develop early penile enlargement. Following adrenarche, DHEA/DHEAS levels increase until the age of 20 to a maximum roughly comparable to that observed at birth. Levels then decline over the next 40 to 60 years to around 20% of peak levels. The clinical significance of this age-related drop is unknown and trials of DHEA/DHEAS replacement in the elderly have not produced convincing benefits. However, in young and old patients with primary adrenal failure, the addition of DHEA/DHEAS to corticosteroid replacement has been shown in some studies to improve mood, energy, and sex drive. Elevated DHEA/DHEAS levels can cause symptoms or signs of hyperandrogenism in women. Men are usually asymptomatic, but through peripheral conversion of androgens to estrogens can occasionally experience mild estrogen excess. Most mild-to-moderate elevations in DHEAS levels are idiopathic. However, pronounced elevations of DHEA/DHEAS may be indicative of androgen-producing adrenal tumors. In small children, congenital adrenal hyperplasia (CAH) due to 3 beta-hydroxysteroid dehydrogenase deficiency is associated with excessive DHEA/DHEAS production. Lesser elevations may be observed in 21-hydroxylase deficiency (the most common form of CAH) and 11 beta-hydroxylase deficiency. By contrast, steroidogenic acute regulatory protein (STAR) or 17 alpha-hydroxylase deficiency is characterized by low DHEA/DHEAS levels. See Steroid Pathways in Special Instructions.

**Useful For:** Diagnosing and differential diagnosis of hyperandrogenism (in conjunction with measurements of other sex steroids) An initial screen in adults might include dehydroepiandrosterone (DHEA)/dehydroepiandrosterone sulfate (DHEAS) and bioavailable testosterone measurement. Depending on results, this may be supplemented with measurements of sex hormone-binding globulin and occasionally other androgenic steroids (eg, 17-hydroxyprogesterone). An adjunct in the diagnosis of...
congenital adrenal hyperplasia (CAH); DHEA/DHEAS measurements play a secondary role to the measurements of cortisol/cortisone, 17 alpha-hydroxyprogesterone, and androstenedione. Diagnosing and differential diagnosis of premature adrenarche

**Interpretation:** Elevated dehydroepiandrosterone (DHEA)/dehydroepiandrosterone sulfate (DHEAS) levels indicate increased adrenal androgen production. Mild elevations in adults are usually idiopathic, but levels >5-fold or more of the upper limit of normal can suggest the presence of an androgen-secreting adrenal tumor. DHEA/DHEAS levels are elevated in >90% of patients with such tumors. This is particularly true for androgen-secreting adrenal carcinomas, as they have typically lost the ability to produce downstream androgens, such as testosterone. By contrast, androgen-secreting adrenal adenomas may also produce excess testosterone and secrete lesser amounts of DHEA/DHEAS. Patients with congenital adrenal hyperplasia (CAH) may show very high levels of DHEA/DHEAS, often 5-fold to 10-fold elevations. However, with the possible exception of 3 beta-hydroxysteroid dehydrogenase deficiency, other steroid analytes offer better diagnostic accuracy than DHEA/DHEAS measurements. Consequently, DHEA/DHEAS testing should not be used as the primary tool for CAH diagnosis. Similarly, discovering a high DHEA/DHEAS level in an infant or child with symptoms or signs of possible CAH should prompt additional testing, as should the discovery of very high DHEA/DHEAS levels in an adult. In the latter case, adrenal tumors need to be excluded and additional adrenal steroid profile testing may assist in diagnosing nonclassical CAH. See Steroid Pathways in Special Instructions.

**Reference Values:**
Premature: <40 ng/mL*
0-1 day: <11 ng/mL*
2-6 days: <8.7 ng/mL*
7 days-1 month: <5.8 ng/mL*
>1-23 months: <2.9 ng/mL*
2-5 years: <2.3 ng/mL
6-10 years: <3.4 ng/mL
11-14 years: <5.0 ng/mL
15-18 years: <6.6 ng/mL
19-30 years: <13 ng/mL
31-40 years: <10 ng/mL
41-50 years: <8.0 ng/mL
51-60 years: <6.0 ng/mL
> or =61 years: <5.0 ng/mL


For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.

**Clinical References:**

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**DHES1**

**Dehydroepiandrosterone Sulfate (DHEA-S), Serum**

**Clinical Information:** Dehydroepiandrosterone (DHEA) is the principal human C-19 steroid. DHEA has very low androgenic potency, but serves as the major direct or indirect precursor for most sex steroids. DHEA is secreted by the adrenal gland and production is at least partly controlled by adrenocorticotropic hormone. The bulk of DHEA is secreted as a 3-sulfoconjugate (DHEA-S). Both
hormones are albumin bound, but binding of DHEA-S is much tighter. In gonads and several other tissues, most notably skin, steroid sulfatases can convert DHEA-S back to DHEA, which can then be metabolized to stronger androgens and to estrogens. During pregnancy, DHEA-S and its 16-hydroxylated metabolites are secreted by the fetal adrenal gland in large quantities. They serve as precursors for placental production of the dominant pregnancy estrogen, estrilol. Within weeks after birth, DHEA-S levels fall by 80% or more and remain low until the onset of adrenarche. Adrenarche is a poorly understood phenomenon peculiar to higher primates, which is characterized by a gradual rise in adrenal androgen production. It precedes puberty but is not causally linked to it. Early adrenarche is not associated with early puberty or with any reduction in final height or overt androgenization and is generally regarded as a benign condition, not needing intervention. However, girls with early adrenarche may be at increased risk of polycystic ovarian syndrome as adults, and some boys may develop early penile enlargement. Following adrenarche, DHEA-S levels increase until the age of 20, up to maximum levels roughly comparable to that observed at birth. Levels then decline over the next 40 to 60 years to around 20% of peak levels. The clinical significance of this age-related drop is unknown and trials of DHEA-S replacement in the elderly have not produced convincing benefits. However, in young and old patients with primary adrenal failure, the addition of DHEA-S to corticosteroid replacement has been shown in some studies to improve mood, energy, and sex drive. Elevated DHEA-S levels can cause symptoms or signs of hyperandrogenism in women. Men are usually asymptomatic, but through peripheral conversion of androgens to estrogens can occasionally experience mild estrogen excess. Most mild to moderate elevations in DHEA-S levels are idiopathic. However, pronounced elevations of DHEA-S may be indicative of androgen-producing adrenal tumors. In small children, congenital adrenal hyperplasia (CAH) due to 3 beta-hydroxysteroid deficiency is associated with excessive DHEA-S production. Lesser elevations may be observed in 21-hydroxylase deficiency (the most common form of CAH) and 11 beta-hydroxylase deficiency. By contrast, steroidogenic acute regulatory protein or 17 alpha-hydroxylase deficiencies are characterized by low DHEA-S levels. An initial workup in adults might also include total and bioavailable testosterone (TTBS / Testosterone, Total and Bioavailable, Serum) measurements. Depending on results, this may be supplemented with measurements of sex hormone-binding globulin (SHBG / Sex Hormone-Binding Globulin [SHBG], Serum) and, occasionally other androgenic steroids (eg, 17-hydroxyprogesterone).

**Useful For:** Diagnosis and differential diagnosis of hyperandrogenism (in conjunction with measurements of other sex steroids) An adjunct in the diagnosis of congenital adrenal hyperplasia

**Diagnosis and differential diagnosis of premature adrenarche**

**Interpretation:** Elevated dehydroepiandrosterone sulfate (DHEA-S) levels indicate increased adrenal androgen production. Mild elevations in adults are usually idiopathic, but levels of 600 mcg/dL or more can suggest the presence of an androgen-secreting adrenal tumor. DHEA-S levels are elevated in more than 90% of patients with such tumors, usually well above 600 mcg/dL. This is particularly true for androgen-secreting adrenal carcinomas, as they have typically lost the ability to produce down-stream androgens, such as testosterone. By contrast, androgen-secreting adrenal adenomas may also produce excess testosterone and secrete lesser amounts of DHEA-S. Patients with congenital adrenal hyperplasia (CAH) may show very high levels of DHEA-S, often 5- to 10-fold elevations. However, with the possible exception of 3 beta-hydroxysteroid dehydrogenase deficiency, other steroid analytes offer better diagnostic accuracy than DHEA-S measurements. Consequently, DHEA-S testing should not be used as the primary tool for CAH diagnosis. Similarly, discovering a high DHEA-S level in an infant or child with symptoms or signs of possible CAH should prompt additional testing, as should the discovery of very high DHEA-S levels in an adult. In the latter case, adrenal tumors need to be excluded and additional adrenal steroid profile testing may assist in diagnosing nonclassical CAH. Girls below the age of 7 to 8 and boys before age 8 to 9, who present with early development of pubic hair, or, in boys, penile enlargement, may be suffering from either premature adrenarche or premature puberty or both. Measurement of DHEA-S (DHES / Dehydroepiandrosterone Sulfate [DHEA-S], Serum), dehydroepiandrosterone (DHEA_ / Dehydroepiandrosterone [DHEA], Serum), and androstenedione (ANST / Androstenedione, Serum), alongside determination of sensitive estradiol (EEST / Estradiol, Serum), testosterone and bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum), or free testosterone (TGRP / Testosterone, Total and Free, Serum), sex hormone-binding globulin (SHBG / Sex Hormone-Binding Globulin [SHBG], Serum), and luteinizing hormone (LH / Luteinizing Hormone [LH], Serum)follicle-stimulating hormone (FSH / Follicle-Stimulating Hormone [FSH], Serum) levels will allow correct diagnosis in most cases. In premature adrenarche, only the adrenal androgens, chiefly
DHEA-S, will be above prepubertal levels, whereas early puberty will also show a fall in SHBG levels and variable elevations of gonadotropins and gonadal sex-steroids above the prepuberty reference range. Levels of DHEA-S do not show significant diurnal variation. Many drugs and hormones can result in changes in DHEA-S levels. Whether any of these secondary changes in DHEA-S levels are of clinical significance and how they should be related to the established normal reference ranges is unknown. In most cases, the drug-induced changes are not large enough to cause diagnostic confusion, but when interpreting mild abnormalities in DHEA-S levels, drug and hormone interactions should be taken into account. Examples of drugs and hormones that can reduce DHEA-S levels include: insulin, oral contraceptive drugs, corticosteroids, central nervous system agents that induce hepatic enzymes (eg, carbamazepine, clomipramine, imipramine, phenytoin), many antilipemic drugs (eg, statins, cholestyramine), domapinergic drugs (eg, levodopa/dopamine, bromocryptine), fish oil, and vitamin E. Drugs that may increase DHEA-S levels include: metformin, troglitazone, prolactin, (and by indirect implication many neuroleptic drugs), danazol, calcium channel blockers (eg, diltiazem, amlodipine), and nicotine.

### Reference Values:

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<tr>
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<th>Age</th>
<th>Reference Range (mcg/dL)</th>
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<tr>
<td>Stage I</td>
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<tr>
<td>Stage II</td>
<td>11.5 years</td>
<td>14-323</td>
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<td>Stage III</td>
<td>13.6 years</td>
<td>5.5-312</td>
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<td>Stage IV</td>
<td>15.1 years</td>
<td>29-412</td>
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<tr>
<td>Stage V</td>
<td>18.0 years</td>
<td>104-468 <em>Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-) 2 years. For boys, there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) is usually reached by age 18. 18-30 years: 105-728 mcg/dL; 31-40 years: 57-522 mcg/dL; 41-50 years: 34-395 mcg/dL; 51-60 years: 20-299 mcg/dL; 61-70 years: 12-227 mcg/dL; &gt; or =71 years: 6.6-162 mcg/dL. FEMALES 1-14 days: DHEA-S levels in newborns are very elevated at birth but fall to prepubertal levels within a few days. Tanner Stages</em></td>
</tr>
</tbody>
</table>

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<tr>
<td>Stage II</td>
<td>10.5 years</td>
<td>22-184</td>
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<tr>
<td>Stage III</td>
<td>11.6 years</td>
<td>11-296</td>
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<tr>
<td>Stage IV</td>
<td>12.3 years</td>
<td>17-343</td>
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<tr>
<td>Stage V</td>
<td>14.5 years</td>
<td>57-395 *Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/-) 2 years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. Progression through Tanner stages is variable. Tanner stage V (adult) is usually reached by age 18. 18-30 years: 83-377 mcg/dL; 31-40 years: 45-295 mcg/dL; 41-50 years: 27-240 mcg/dL; 51-60 years: 16-195 mcg/dL; 61-70 years: 9.7-159 &gt; or =71 years: 5.3-124 mcg/dL.</td>
</tr>
</tbody>
</table>
**Clinical References:**

**Dementia, Autoimmune Evaluation, Serum**

**Clinical Information:** The rapid identification of subacute cognitive decline as autoimmune dementia facilitates optimum treatment with immunotherapy and an expedited search for a limited stage of cancer in some patients. Traditionally, neurologists have been reluctant to consider a diagnosis of an autoimmune cognitive disorder in the absence of delirium. However, some recent case series and clinical-serologic observations have suggested a growing appreciation for autoimmune neurologic disorders presenting with features of a rapidly progressive dementia rather than delirium. These disorders can affect all age groups. Unfortunately, these potentially reversible conditions may be misdiagnosed as being progressive neurodegenerative (currently irreversible) disorders, with devastating consequences for the patient. In the evaluation of a patient with cognitive decline, clinicians should consider the possibility of an autoimmune etiology on their list of differential diagnoses. The importance of not overlooking this possibility rests in the experience that these patients have a potentially immunotherapy responsive, reversible disorder. The development and widespread availability of neural antibody marker testing has changed this perspective so that other presenting symptoms such as personality change, executive dysfunction, and psychiatric symptoms are increasingly recognized in an autoimmune context. Clues that are helpful in identifying patients with an autoimmune dementia can be summarized within a triad of: 1) suspicious clinical features (a subacute onset of symptoms, a rapidly progressive course, and fluctuating symptoms) and radiological findings, 2) the detection of cerebral spinal fluid (CSF) or serological biomarkers of autoimmunity and 3) a response to immunotherapy. Detection of neural autoantibodies in serum or CSF serves 2 purposes; to inform the physician of a likely autoimmune etiology and to raise suspicion for a paraneoplastic cause. The neurological associations of neural autoantibodies tend to be diverse and multifocal, although certain syndromic associations may apply. For example, neuronal voltage-gated potassium channel (VGKC) antibodies were initially considered to be specific for autoimmune limbic encephalitis or disorders of peripheral nervous hyperexcitability, but over time other presentations have been reported, including a rapidly progressive course of cognitive decline mimicking frontotemporal dementia and Creutzfeldt-Jakob disease. Since neurological presentations are often multifocal and diverse, comprehensive antibody testing is usually more informative than testing for 1 or 2 selected antibodies. Some of the antibodies are highly predictive of an unsuspected underlying cancer. For example; small-cell lung carcinoma (antineuronal nuclear antibody-type 1, ANNA-1; collapsin response-mediator protein-5 neuronal, CRMP-5 IgG), ovarian teratoma (N-methyl-D-aspartate receptor, NMDA-R), and thymoma (CRMP-5 IgG). Also, a profile of seropositivity for multiple autoantibodies may be informative for cancer type. For example, in a patient presenting with a rapidly progressive dementia who has muscle acetylcholine receptor (AChR) binding, alpha 3 ganglionic AChR, and CRMP 5 IgG, those findings should raise a high suspicion for thymoma. If an associated tumor is found, its resection or ablation optimizes the neurological outcome. Antibody testing on CSF is additionally helpful particularly when serum testing is negative. However, simultaneous testing of serum and CSF is recommended for NMDA-R antibody, because CSF is usually more informative.

**Useful For:** Investigating new onset dementia and cognitive impairment plus 1 or more of the
following: -Rapid onset and progression -Fluctuating course -Psychiatric accompaniments (psychosis, hallucinations) -Movement disorder (myoclonus, tremor, dyskinesias) -Headache -Autoimmune stigmata (personal history or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, poliosis [premature graying], myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus) -Smoking history (20+ pack years) or other cancer risk factors -History of cancer -Inflammatory cerebral spinal fluid -Neuroimaging findings atypical for degenerative etiology

**Interpretation:** Antibodies specific for neuronal, glial, or muscle proteins are valuable serological markers of autoimmune epilepsy and of a patient's immune response to cancer. These autoantibodies are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. It is not uncommon for more than 1 of the following autoantibodies to be detected in patients with autoimmune dementia: -Plasma membrane antibodies (N-methyl-D-aspartate (NMDA) receptor; 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid (AMPA) receptor; gamma-amino butyric acid (GABA-B) receptor). These autoantibodies are all potential effectors of dysfunction. -Neuronal nuclear autoantibody, type 1 (ANNA-1) or type 3 (ANNA-3). -Neuronal or muscle cytoplasmic antibodies (amphiphysin, Purkinje cell antibody-type 2 [PCA-2], collapsin response-mediator protein-5 neuronal [CRMP-5-IgG], or glutamic acid decarboxylase [GAD65] antibody).

**Reference Values:**

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</thead>
<tbody>
<tr>
<td>Paraneoplastic Western Blot Negative</td>
</tr>
<tr>
<td>CRMP-5-IgG Western Blot Negative</td>
</tr>
<tr>
<td>Amphiphysin Western Blot Negative</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ISLET CELL ANTIBODIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamic Acid Decarboxylase (GAD65) Antibody</td>
</tr>
<tr>
<td>&lt; or =0.02 nmol/L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CATION CHANNEL ANTIBODIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Type Calcium Channel Antibody</td>
</tr>
<tr>
<td>&lt; or =0.03 nmol/L</td>
</tr>
<tr>
<td>P/Q-Type Calcium Channel Antibody</td>
</tr>
<tr>
<td>&lt; or =0.02 nmol/L</td>
</tr>
</tbody>
</table>
AChR Ganglionic Neuronal Antibody
< or =0.02 nmol/L
Neuronal VGKC Autoantibody
< or =0.02 nmol/L

ACHR RECEPTOR ANTIBodies
ACh Receptor (Muscle) Binding Antibody
< or =0.02 nmol/L

N-Methyl-D-aspartate receptor (NMDA-R) CBA
Negative
IFA: <1:120
2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid receptor (AMPA-R) CBA
Negative
IFA: <1:120
Gamma-Amino Butyric acid-type B receptor (GABA-B-R) CBA
Negative
IFA: <1:120
Neuromyelitis Optica (NMO)/Aquaporin-4-IgG FACS Assay
Negative
LGII-IgG CBA: Negative
CASPR2-IgG CBA: Negative


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**Dementia, Autoimmune Evaluation, Spinal Fluid**

**Clinical Information:** The rapid identification of subacute cognitive decline as autoimmune dementia facilitates optimum treatment with immunotherapy and an expedited search for a limited stage of cancer in some patients. Traditionally, neurologists have been reluctant to consider a diagnosis of an autoimmune cognitive disorder in the absence of delirium. However, some recent case series and clinical-serologic observations have suggested a growing appreciation for autoimmune neurologic disorders presenting with features of a rapidly progressive dementia rather than delirium. These disorders can affect all age groups. Unfortunately, these potentially reversible conditions may be misdiagnosed as being progressive neurodegenerative (currently irreversible) disorders, with devastating consequences for the patient. In the evaluation of a patient with cognitive decline, clinicians should consider the possibility of an autoimmune etiology on their list of differential diagnoses. The importance of not overlooking this possibility rests in the experience that these patients have a potentially immunotherapy-responsive, reversible disorder. The development and widespread availability of neural antibody marker testing has changed this perspective so that other presenting symptoms such as personality change, executive dysfunction, and psychiatric symptoms are increasingly recognized in an autoimmune context. Clues that are helpful in identifying patients with an autoimmune dementia can be summarized within a triad of: 1) suspicious clinical features (a subacute onset of symptoms, a rapidly progressive course, and fluctuating symptoms) and radiological findings, 2) the detection of cerebral spinal fluid (CSF) or serological biomarkers of autoimmunity and 3) a response to immunotherapy. Detection of neural autoantibodies in serum or CSF serves 2 purposes; to inform the physician of a likely autoimmune etiology, and to raise suspicion for a paraneoplastic cause. The neurological associations of neural autoantibodies tend to be diverse and multifocal, although certain syndromic associations may apply. For example, neuronal voltage-gated potassium channel (VGKC) antibodies were initially considered to be specific for autoimmune limbic encephalitis or disorders of
Peripheral nervous hyperexcitability, but over time other presentations have been reported, including a rapidly progressive course of cognitive decline mimicking frontotemporal dementia and Creutzfeldt-Jakob disease. Since neurological presentations are often multifocal and diverse, comprehensive antibody testing is usually more informative than testing for 1 or 2 selected antibodies. Some of the antibodies are highly predictive of an unsuspected underlying cancer. For example; small-cell lung carcinoma (antineuronal nuclear antibody-type 1, ANNA-1), collapsin response-mediator protein-5 neuronal, CRMP-5 IgG), ovarian teratoma (N-methyl-D-aspartate receptor, NMDA-R), and thymoma (CRMP-5 IgG). Also, a profile of seropositivity for multiple autoantibodies may be informative for cancer type. For example, in a patient presenting with a rapidly progressive dementia who has muscle acetylcholine receptor (AChR) binding, alpha 3 ganglionic AchR, and CRMP 5 IgG, the findings should raise a high suspicion for thymoma. If an associated tumor is found, its resection or ablation optimizes the neurological outcome. Antibody testing on CSF is additionally helpful particularly when serum testing is negative. However, simultaneous testing on serum and CSF is recommended for some (such as NMDA-R antibody testing, since CSF is usually more informative).

**Useful For:** Investigating new onset dementia and cognitive impairment plus 1 or more of the following accompaniments: Rapid onset and progression Fluctuating course Psychiatric accompaniments (psychosis, hallucinations) Movement disorder (myoclonus, tremor, dyskinesias) Headache Autoimmune stigmata (personal history or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, poliosis [premature graying], myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus) Smoking history (20+ pack years) or other cancer risk factors History of inflammatory cerebral spinal fluid Neuroimaging findings atypical for degenerative etiology

**Interpretation:** Antibodies specific for neuronal, glial, or muscle proteins are valuable serological markers of autoimmune epilepsy and of a patient's immune response to cancer. These autoantibodies are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. It is not uncommon for more than 1 of the following autoantibodies to be detected in patients with autoimmune dementia: - Plasma membrane antibodies (N-methyl-D-aspartate (NMDA) receptor; 2-aminoo-3-(5-methyl-3-oxo-1,2- oxazol-4-yl) propanoic acid (AMPA) receptor; gamma-aminobutyric acid (GABA-B) receptor). These autoantibodies are all potential effectors of dysfunction. - Neuronal nuclear autoantibody type 1 (ANNA-1) or type 3 (ANNA-3). - Neuronal or muscle cytoplasmic antibodies (amphiphysin, Purkinje cell antibody-type 2 [PCA-2], collapsin response-mediator protein-5 neuronal [CRMP-5-IgG], or glutamic acid decarboxylase [GAD65] antibody).

**Reference Values:**
- Anti-neuronal Nuclear Ab, Type 1 (ANNA-1), CSF: <1:2
- Anti-neuronal Nuclear Ab, Type 2 (ANNA-2), CSF: <1:2
- Anti-neuronal Nuclear Ab, Type 3 (ANNA-3), CSF: <1:2
- Purkinje Cell Cytoplasmic Ab, Type1 (PCA-1), CSF: <1:2
- Purkinje Cell Cytoplasmic Ab, Type 2 (PCA-2), CSF: <1:2
- Purkinje Cell Cytoplasmic Ab, Type Tr (PCA-Tr), CSF: <1:2
- Amphiphysin Ab, CSF: <1:2
- CRMP-5-IgG Ab, CSF: <1:2
- Paraneoplastic Western Blot, CSF: Negative
- CRMP-5-IgG Western Blot, CSF: Negative
- Amphiphysin Western Blot, CSF: Negative
- Glutamic Acid Decarboxylase-65 (GAD65), CSF: < or =0.02 nmol/L
- Neuronal Voltage-Gated Potassium Channel-Complex Autoantibody, Spinal Fluid: < or =0.02 nmol/L
- N-Methyl-D-aspartate receptor (NMDA-R), CSF
  - CBA: Negative
  - IFA: <1:2
- 2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl) propanoic acid receptor (AMPA-R), CSF
  - CBA: Negative
  - IFA: <1:2
- Gamma-Amino Butyric acid-type B receptor (GABA-B-R), CSF
  - CBA: Negative
  - IFA: <1:2
- Anti-Glial/Neuronal Nuclear Ab, Type 1 (AGNA-1), CSF: <1:2
- Neuromyelitis Optica (NMO)/Aquaporin-4-IgG FACS Assay, CSF
**Clinical References:**

**Dengue Virus Antibody, IgG and IgM, Serum**

**Clinical Information:** Dengue virus (DV) is a globally distributed flavivirus with 4 distinct serotypes (DV-1, -2, -3, -4) and is primarily transmitted by the Aedes aegypti mosquito, which is found throughout the tropical and subtropical regions of over 100 countries. DV poses a significant worldwide public health threat with approximately 2.5 to 3 billion people residing in DV endemic areas, among whom 100 to 200 million individuals will be infected and approximately 30,000 patients will succumb to the disease, annually. Following dengue infection, the incubation period varies from 3 to 7 days and while some infections remain asymptomatic, the majority of individuals will develop classic dengue fever. Symptomatic patients become acutely febrile and present with severe musculoskeletal pain, headache, retro-orbital pain, and a transient macular rash, most often observed in children. Fever defervescence signals disease resolution in most individuals. However, children and young adults remain at increased risk for progression to dengue hemorrhagic fever and dengue shock syndrome, particularly during repeat infection with a new DV serotype. Detection of dengue-specific IgM/IgG-class antibodies remains the most commonly utilized diagnostic method. Seroconversion occurs approximately 3 to 7 days following exposure and, therefore, testing of acute and convalescent sera may be necessary to make the diagnosis. As an adjunct to serologic testing, identification of early DV infection may be made by detection of the DV NS1 antigen. NS1 antigenemia is detectable within 24 hours of infection and up to 9 days following symptom onset. The DV NS1 antigen can be detected by ordering DNSAG / Dengue Virus NS1 Antigen, Serum.

**Useful For:** Aids in the diagnosis of dengue virus infection

**Interpretation:**
- **IgG:** The presence of IgG-class antibodies to dengue virus (DV) is consistent with exposure to this virus sometime in the past. By 3 weeks following exposure, nearly all immunocompetent individuals should have developed IgG antibodies to DV. **IgM:** The presence of IgM-class antibodies to DV is consistent with acute-phase infection. IgM antibodies become detectable 3 to 7 days following infection and may remain detectable for up to 6 months or longer following disease resolution. The absence of IgM-class antibodies to DV is consistent with lack of infection. However, specimens drawn too soon following exposure may be negative for IgM antibodies to DV. If DV remains suspected, a second specimen, drawn approximately 10 to 12 days following exposure should be tested.

**Reference Values:**
- **IgG:** negative
- **IgM:** negative

**Clinical References:**
Dengue Virus Antibody/Antigen Panel, Serum

Clinical Information: Dengue virus (DV) is a globally distributed flavivirus with 4 distinct serotypes (DV-1, -2, -3, -4) and is primarily transmitted by the Aedes aegypti mosquito, which is found throughout the tropical and subtropical regions of over 100 countries. DV poses a significant worldwide public health threat with approximately 2.5 to 3 billion people residing in DV endemic areas, among whom 100 to 200 million individuals will be infected and approximately 30,000 patients will succumb to the disease, annually. Following dengue infection, the incubation period varies from 3 to 7 days and while some infections remain asymptomatic, the majority of individuals will develop classic dengue fever. Symptomatic patients become acutely febrile and present with severe musculoskeletal pain, headache, retro-orbital pain, and a transient macular rash, most often observed in children. Fever defervescence signals disease resolution in most individuals. However, children and young adults remain at increased risk for progression to dengue hemorrhagic fever and dengue shock syndrome, particularly during repeat infection with a new DV serotype. Detection of dengue-specific IgM/IgG-class antibodies remains the most commonly utilized diagnostic method. Seroconversion occurs approximately 3 to 7 days following exposure and therefore testing of acute and convalescent sera may be necessary to make the diagnosis. Detection of the DV nonstructural protein 1 (NS1) has emerged as an alternative biomarker to both serologic- and molecular-based techniques for diagnosis of acute DV infection. NS1 antigenemia is detectable within 24 hours and up to 9 days following symptoms onset. This overlaps with the DV viremic phase and NS1 is often detectable prior to IgM seroconversion. Concurrent evaluation (as performed in this profile) for the NS1 antigen alongside testing for IgM- and IgG-class antibodies to DV provides optimal diagnostic potential for both early and late dengue disease.

Useful For: Aids in the diagnosis of dengue virus infection

Interpretation: IgG: The presence of IgG-class antibodies to dengue virus (DV) is consistent with exposure to this virus sometime in the past. By 3 weeks following exposure, nearly all immunocompetent individuals should have developed IgG antibodies to DV. IgM: The presence of IgM-class antibodies to DV is consistent with acute-phase infection. IgM antibodies become detectable 3 to 7 days following infection and may remain detectable for up to 6 months or longer following disease resolution. The absence of IgM-class antibodies to DV is consistent with lack of infection. However, specimens drawn too soon following exposure may be negative for IgM antibodies to DV. If DV remains suspected, a second specimen, drawn approximately 10 to 12 days following exposure should be tested. Nonstructural protein 1 (NS1): The presence of dengue NS1 antigen is consistent with acute-phase infection with dengue virus. The NS1 antigen is typically detectable within 1 to 2 days following infection and up to 9 days following symptom onset. NS1 antigen may also be detectable during secondary dengue virus infection, but for a shorter duration of time (1-4 days following symptom onset). The absence of dengue NS1 antigen is consistent with the lack of acute-phase infection. The NS1 antigen may be negative is samples collected immediately following dengue virus infection (<24-48 hours) and is rarely detectable following 9 to 10 days of symptoms.

Reference Values:
IgG: negative
IgM: negative
NS1: negative
Reference values apply to all ages.

**Clinical Information:** Dengue virus (DV) is a globally distributed flavivirus with 4 distinct serotypes (DV-1, -2, -3, -4) and is primarily transmitted by the Aedes aegypti mosquito, found throughout the tropical and subtropical regions of over 100 countries. DV poses a significant worldwide public health threat with approximately 2.5 to 3 billion people residing in DV endemic areas, among whom 100 to 200 million individuals will be infected and approximately 30,000 patients will succumb to the disease, annually. Following dengue infection, the incubation period varies from 3 to 7 days and while some infections remain asymptomatic, the majority of individuals will develop classic dengue fever. Symptomatic patients become acutely febrile and present with severe musculoskeletal pain, headache, retro-orbital pain, and a transient macular rash, most often observed in children. Fever defervescent signals disease resolution in most individuals. However, children and young adults remain at increased risk for progression to dengue hemorrhagic fever and dengue shock syndrome, particularly during repeat infection with a new DV serotype. Detection of the DV nonstructural protein 1 (NS1) has emerged as an alternative biomarker to both serologic and molecular based techniques for diagnosis of acute DV infection. NS1 antigenemia is detectable within 24 hours and up to 9 days following symptoms onset. This overlaps with the DV viremic phase and NS1 is often detectable prior to IgM seroconversion. Concurrent evaluation for the NS1 antigen alongside testing for IgM- and IgG-class antibodies to DV (DENG) provides optimal diagnostic potential for both early and late dengue disease.

**Useful For:** An aid in the diagnosis of dengue virus infection

**Interpretation:** Positive: The presence of dengue nonstructural protein 1 (NS1) antigen is consistent with acute-phase infection with dengue virus. The NS1 antigen is typically detectable within 1 to 2 days following infection and up to 9 days following symptom onset. NS1 antigen may also be detectable during secondary dengue virus infection, but for a shorter duration of time (1-4 days following symptom onset). Negative: The absence of dengue NS1 antigen is consistent with the lack of acute-phase infection. The NS1 antigen may be negative if specimen is collected immediately following dengue virus infection (<24-48 hours) and is rarely detectable following 9 to 10 days of symptoms.

**Reference Values:**

Negative

Reference values apply to all ages.

**Clinical References:**

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**Dentatorubral-Pallidoluysian Atrophy (DRPLA) Gene Analysis**

**Clinical Information:** Dentatorubral-pallidoluysian atrophy (DRPLA) is a rare autosomal dominant neurodegenerative disorder characterized by ataxia, choreoathetosis, dementia, and psychiatric disturbance in adults and ataxia, myoclonus, seizures, and progressive intellectual deterioration in children. Characteristic neuropathologic observations include degeneration of the dentatorubral and pallidoluysian systems of the central nervous system. The prevalence of DRPLA depends on the geographic and ethnic origin of the population being studied. DRPLA was first described in a European individual without a family history; however, it is predominantly found as an inherited condition and is most prevalent in Japan (0.2-0.7 per 100,000). Although rare, DRPLA has been identified in other populations including Europe and North America. DRPLA is caused by an expansion of the CAG trinucleotide repeat in the ATN1 (DRPLA) gene. This trinucleotide repeat is polymorphic in the general population, with the number of repeats ranging from 7 to 35. In affected individuals the CAG expansion ranges from 48 to 93 repeats. As with other trinucleotide repeat disorders, anticipation is frequently observed, and larger CAG expansions are associated with earlier onset and a more severe and rapid clinical course. In DRPLA, the observed anticipation appears to be significantly greater in paternal transmissions.

**Useful For:** Molecular confirmation of a diagnosis of dentatorubral-pallidoluysian atrophy (DRPLA)
for symptomatic patients. Predictive testing for individuals with a family history of DRPLA and a documented expansion in the ATN1 gene in an affected family member.

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Normal alleles: 7-35 CAG repeats
Abnormal alleles: 49-93 CAG repeats
An interpretive report will be provided.

**Clinical References:**

**Deoxypyridinoline Crosslinks, Urine**

**Reference Values:**
Deoxypyridinoline Urine-ratio to CRT
- Adult Male: 2.3 â€“ 8.7 nmol/mmol
- Premenopausal Adult Female: 3.1 â€“ 8.7 nmol/mmol

Creatinine, Urine â€“ per volume
- No reference interval

The target value for treated post-menopausal adult females is the same as the Premenopausal reference interval.

**Dermatophagoides microceras, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L
- Interpretation
  - 0: Negative

DermPath Consultation, Wet Tissue

Clinical Information: Dermatopathology involves histologic examination of skin biopsy and oral mucosal specimens.

Useful For: Histologic diagnosis and differential diagnosis of cutaneous diseases

Interpretation: Histologic diagnosis is based primarily on interpretation of hematoxylin and eosin-stained sections. Special histochemical stains, such as alcian blue, Giemsa, or periodic acid-Schiff may be necessary in some cases. Interpretation is based on evaluation of patterns including architectural and cytologic details, which are included in a microscopic description.

Reference Values: Diagnosis and description of microscopic findings


Des-Gamma-Carboxy Prothrombin (DCP), Serum

Clinical Information: Des-gamma-carboxy prothrombin (DCP), also known as the protein induced by vitamin K absence or antagonist II (PIVKA-II), is an abnormal form of the coagulation protein, prothrombin. DCP is a nonfunctional prothrombin resulting from a lack of carboxylation of 10 glutamic acid residues in the N-terminal portion of the molecule. In normal liver, prothrombin undergoes post-translational carboxylation before release into the peripheral blood. The carboxylation converts specific amino-terminal glutamic acid residues to gamma-carboxyglutamic acid. The vitamin K dependent carboxylase responsible for the carboxylation is absent in many hepatocellular carcinoma (HCC) cells, and an abnormal prothrombin with all or some of unconverted glutamic acid is secreted. Therefore, this noncarboxylated form (DCP) has been used as an HCC biomarker. DCP is considered a complementary biomarker to alpha fetoprotein (AFP) and third electrophoretic form of lentil lectin-reactive AFP% (AFP-L3%) for assessing the risk of developing HCC. The elevation of both AFP-L3 and DCP indicate progression of HCC, albeit they reflect different features of the progression. In a prospective study of patients in the United States with an established diagnosis of HCC, the sensitivities for AFP, AFP-L3%, and DCP were 68%, 62%, and 73%, respectively. When the 3 markers were combined, the sensitivity was 86%. In another study, DCP levels were shown to correlate with tumor size and metastatic HCC. In this study, compared to AFP and AFP-L3%, DCP had the highest sensitivity (87%) and the highest positive predictive value (87%) in patients with HCC due to chronic hepatitis B and C infections. A number of studies have shown that elevated serum DCP is significantly related to portal vein invasion and/or intrahepatic metastasis, which significantly affect prognosis for patients with HCC. DCP can be elevated in other conditions besides HCC. Conditions such as obstructive jaundice, intrahepatic cholestasis causing chronic decrease in vitamin K, and ingestion of drugs such as warfarin or wide-spectrum antibiotics can...
result in high concentrations of DCP. In addition, 25% to 50% of patients with HCC will have a DCP value within the reference range. Because of this, a normal DCP value does not rule out HCC.

**Useful For:** Risk assessment of patients with chronic liver disease for development of hepatocellular carcinoma (HCC). An aid in the monitoring of HCC patients post therapy if des-gamma-carboxy prothrombin (DCP) level was elevated prior to therapy. An elevated DCP level is associated with increased risk of recurring HCC.

**Interpretation:** In patients with an elevated des-gamma-carboxy prothrombin (DCP) result (> or =7.5 ng/mL), the risk of developing hepatocellular carcinoma (HCC) is 36.5% (95% CI 23.5%-49.6%). The risk of developing HCC with a negative DCP result (<7.5 ng/mL) is 7.6% (95% CI 4.4%-10.8%).

**Reference Values:**
<7.5 ng/mL


**Desipramine, Serum**

**Clinical Information:** Desipramine is a tricyclic antidepressant; it also is a metabolite of imipramine. These drugs have also been employed in the treatment of enuresis (involuntary urination) in childhood and severe obsessive-compulsive neurosis. Desipramine is the antidepressant of choice in patients where maximal stimulation is indicated. The therapeutic concentration of desipramine is 100 to 300 ng/mL. About 1 to 3 weeks of treatment are required before therapeutic effectiveness becomes apparent. The most frequent side effects are those attributable to anticholinergic effects: dry mouth, constipation, dizziness, tachycardia, palpitations, blurred vision, and urinary retention. These occur at blood concentrations in excess of 400 ng/mL, although they may occur at therapeutic concentrations in the early stage of therapy. Cardiac toxicity (first-degree heart block) is usually associated with blood concentrations in excess of 400 ng/mL.

**Useful For:** Monitoring serum concentration during therapy Evaluating potential toxicity The test may also be useful to evaluate patient compliance

**Interpretation:** Most individuals display optimal response to desipramine with serum levels of 100 to 300 ng/mL. Some individuals may respond well outside of this range, or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Risk of toxicity is increased with levels above 400 ng/mL.

**Reference Values:**
Therapeutic concentration: 100-300 ng/mL

Desmin Immunostain, Technical Component Only

**Clinical Information:** Desmin is an intermediate filament protein in muscle cells. In normal tissues, the antibody reacts with both striated and smooth muscle cells. This labeling is confined to the Z band in skeletal and cardiac muscle giving a characteristic striated appearance. In neoplastic tissues, the antibody reacts with tumors of myogenic origin such as those arising from smooth muscle (leiomyosarcomas) and those derived from striated muscle (rhabdomyosarcomas).

**Useful For:** Aids in the identification of striated and smooth muscle cells and tumors derived from this cell type

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

Desmoglein 1 (DSG1) and Desmoglein 3 (DSG3), IgG Antibodies, Serum

**Clinical Information:** Pemphigus includes a group of often fatal autoimmune, blistering diseases characterized by intraepithelial lesions. Pemphigus vulgaris and its variants may present with oral or mucosal lesions alone or with mucosal plus skin lesions. Pemphigus foliaceous and variants present with skin lesions alone. Indirect immunofluorescence (IIF) studies reveal that both forms of pemphigus are caused by autoantibodies to cell surface antigens of stratified epithelia or mucous membranes and skin. These antibodies bind to calcium-dependent adhesion molecules in cell surface desmosomes, notably desmoglein 1 (DSG1) in pemphigus foliaceous and desmoglein 3 (DSG3) and/or DSG1 in pemphigus vulgaris. Desmogleins are protein substances located in and on the surface of keratinocytes. These proteins have been shown to be a critical factor in cell-to-cell adhesion. Antibodies to desmogleins can result in loss of cell adhesion, the primary cause of blister formation in pemphigus. The diagnosis of pemphigus depends on biopsy and serum studies that characterize lesions and detect the autoantibodies that cause them. Originally, the serum studies were performed by IIF using monkey esophagus and other tissue substrates. The identification of the reactive antigens as DSG1 and DSG3 has made it possible to develop highly specific and sensitive enzyme-linked immunosorbent assay methods.

**Useful For:** Preferred screening test for patients suspected to have an autoimmune blistering disorder of the skin or mucous membranes (pemphigus) As an aid in the diagnosis of pemphigus

**Interpretation:** Antibodies to desmoglein 1 (DSG1) and desmoglein 3 (DSG3) have been shown to be present in patients with pemphigus. Many patients with pemphigus foliaceous, a superficial form of pemphigus have antibodies to DSG1. Patients with pemphigus vulgaris, a deeper form of pemphigus, have antibodies to DSG3 and sometimes DSG1 as well. Antibody titer correlates in a semiquantitative manner with disease activity in many patients. Patients with severe disease can usually be expected to
have high titers of antibodies to DSG. Titers are expected to decrease with clinical improvement. Our experience demonstrates a very good correlation between DSG1 and DSG3 results and the presence of pemphigus. Adequate sensitivities and specificity for disease are documented. However, in those patients strongly suspected to have pemphigus either by clinical findings or by routine biopsy, and in whom the DSG assay is negative, the IIF test (CIFS / Cutaneous Immunofluorescence Antibodies [IgG], Serum) is recommended.

**Reference Values:**

**DESMOGLEIN 1**
- <14.0 U (negative)
- 14.0-20.0 U (indeterminate)
- >20.0 U (positive)

**DESMOGLEIN 3**
- <9.0 U (negative)
- 9.0-20.0 U (indeterminate)
- >20.0 U (positive)


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**DSG3 (DSG3) Immunostain, Technical Component Only**

**Clinical Information:** Desmosomes are intercellular junctions between epithelial, myocardial, and certain other cell types. Desmoglein 3 (DSG3) is a calcium-binding transmembrane glycoprotein component of desmosomes in vertebrate epithelial cells. Currently, 3 desmoglein subfamily members have been identified and all are members of the cadherin cell adhesion molecule superfamily. DSG3 is the auto antigen targeted by the immune system in the blistering skin disease pemphigus vulgaris. Positivity for DSG3 in a non-small cell lung carcinoma supports a diagnosis of squamous cell carcinoma.

**Useful For:** Classification of squamous cell carcinomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:** Wahl JK 3rd: Generation of monoclonal antibodies specific for desmoglein family members. Hybrid Hybridomics 2002;21:37-44

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**DSRCT (Desmoplastic Small Round-Cell Tumor by Reverse Transcriptase PCR (RT-PCR))**
Clinical Information: Desmoplastic small round-cell tumor (DSRCT) is a member of the small round-cell tumor group that also includes rhabdomyosarcoma, synovial sarcoma, lymphoma, Wilms tumor, and Ewing sarcoma. DSRCT is a type of sarcoma that affects mainly children and adolescent males, usually in the form of widespread intra-abdominal growth not related to any specific organ system. The tumor is composed of angulated nests of small round cells with an abundant desmoplastic stroma. The tumor cells show multiphenotypic differentiation and are usually positive for cytokeratin and desmin. These tumors can express renal, epithelial, muscle, and endocrine markers. While treatment and prognosis depend on establishing the correct diagnosis, the diagnosis of sarcomas that form the small round-cell tumor group can be very difficult by light microscopic examination alone, especially true when only small-needle biopsy specimens are available for examination. The use of histochemical and immunohistochemical stains (eg, desmin, cytokeratin, and WT1) can assist in establishing the correct diagnosis, they cannot distinguish between DSRCT and other small round-cell tumors. Expertise in soft tissue and bone pathology are often needed. Studies have shown that some sarcomas have specific recurrent chromosomal translocations. These translocations produce highly specific gene fusions that help define and characterize subtypes of sarcomas and are useful in the diagnosis of these lesions. DSRCT is associated with a unique chromosomal translocation t(11:22)(p13;q12) that involves the EWSR1 and the WT1 genes. EWSR1 is the breakpoint site of translocations associated with Ewing sarcoma and WT1 is a gene altered in some Wilms tumors. The translocation results in a fusion of the 2 genes with expression of a chimeric EWSR1-WT1 product. The most common breakpoints involve the intron between EWSR1 exon 7 and 8 and the intron between WT1 exons 7 and 8. Analyses of these transcripts have shown an in-frame fusion of RNA encoding the amino-terminal domain of EWSR1 to the zinc finger of the DNA-binding domain of WT1.

Useful For: Supporting the diagnosis of desmoplastic small round-cell tumor

Interpretation: A positive EWSR1-WT1 result is consistent with a diagnosis of desmoplastic small round-cell tumor (DSRCT). Sarcomas other than DSRCT, and carcinomas, melanomas, and lymphomas are negative for the fusion products. A negative result does not rule out a diagnosis of DSRCT.

Reference Values: An interpretative report will be provided.


Dexamethasone

Reference Values:
Units = ng/dL

Adults baseline: <30
8:00 AM following 1 mg dexamethasone previous evening: 140 - 295
8:00 AM following 8 mg dexamethasone (4 x 2 mg doses) previous day: 1600 - 2850

Dexedrine (Dextroamphetamine)

Reference Values:
Reference Range: 10 – 100 ng/mL
Dextromethorphan (DM), Serum

Reference Values:
Reference Range: 2.0 - 6.0 ng/mL

Diabetes Mellitus Type 1 Evaluation, Serum

Clinical Information: Islet cell autoantibodies have been known to be associated with type 1 diabetes mellitus since the 1970s. Since 1988, several autoantigens against which islet antibodies are directed have been identified. These include the insulinoma-associated protein 2 (IA-2), glutamic acid decarboxylase 65 (GAD65), insulin and, most recently, the zinc transporter ZnT8. Only 4% to 7% of patients with type 1 diabetes are autoantibody negative, fewer than 10% have only 1 marker, and around 70% have 3 or 4 markers. These findings have been confirmed in multiple specialty laboratories internationally. One or more of these autoantibodies are detected in 93% to 96% of patients with type 1 diabetes, both adults and children. These antibodies are also detectable in relatives of type 1 diabetic patients at risk for developing diabetes, before clinical onset. Some patients with type 1 diabetes are initially diagnosed as having type 2 diabetes because of symptom-onset in adulthood, societal obesity, and initial insulin-independence. These patients with either "latent autoimmune diabetes in adulthood" or type 1 diabetes mellitus may be distinguished from those patients with type 2 diabetes by detection of 1 or more islet autoantibodies (including ZnT8 antibody). Patients with gestational diabetes can also be stratified for future diabetes risk by detection of 1 or more islet autoantibodies.

Useful For: Distinguishing type 1 from type 2 diabetes mellitus Identifying individuals at risk of type 1 diabetes (including high-risk relatives of patients with diabetes) Predicting future insulin requirement treatment in patients with adult-onset diabetes

Interpretation: Seropositivity for 1 or more islet cell autoantibodies is supportive of: -A diagnosis of type 1 diabetes. Only 2% to 4% of patients with type 1 diabetes are antibody negative; 90% have more than 1 antibody marker, and 70% have 3 or 4 markers. Patients with gestational diabetes who are antibody seropositive are at high risk for diabetes postpartum. Rarely, diabetic children test seronegative, which may indicate a diagnosis of maturity-onset diabetes of the young in clinically suspicious cases. -A high risk for future development of diabetes. Among 44 first-degree relatives of patients with type 1 diabetes, those with 3 antibodies had a 70% risk of developing type 1 diabetes within 5 years. -A current or future need for insulin therapy in patients with diabetes. In the UK Prospective Diabetes Study, 84% of those classified clinically as having type 2 diabetes and seropositive for glutamic acid decarboxylase 65 required insulin within 6 years, compared to 14% that were antibody negative.

Reference Values:
GLUTAMIC ACID DECARBOXYLASE (GAD65) ANTIBODY
< or =0.02 nmol/L
Reference values apply to all ages.
INSULIN ANTIBODIES
< or =0.02 nmol/L
Reference values apply to all ages.
ISLET ANTIGEN 2 (IA-2) ANTIBODY
< or =0.02 nmol/L
Reference values apply to all ages.
ZINC Transporter 8 (ZnT8) ANTIBODY
< 15.0 U/mL
Reference values apply to all ages.

Diazepam and Nordiazepam, Serum

**Clinical Information:** Diazepam, a benzodiazepine derivative, is an anxiolytic agent that reduces neuronal depolarization resulting in decreased action potentials. It enhances the action of gamma-aminobutyric acid (GABA) by tightly binding to A-type GABA receptors, thus opening the membrane channels and allowing the entry of chloride ions. It is also used as a muscle relaxant, procedural sedation agent, and sedative-hypnotic agent to treat withdrawal states (i.e., ethanol), along with other conditions (seizures). Diazepam is metabolized to several metabolites in the liver including temazepam, oxazepam, and nordiazepam (desmethyldiazepam) and the clearance of the drug is reduced considerably in the elderly and in patients with hepatic disease. Therapeutic assessment typically includes measurement of both the parent drug (diazepam) and the active metabolite (nordiazepam).

**Useful For:** Assessing compliance Monitoring for appropriate therapeutic level Assessing toxicity

**Interpretation:** For seizures: Serum concentrations are not usually monitored during early therapy because response to the drug can be monitored clinically as seizure control. If seizures resume despite adequate therapy, another anticonvulsant must be considered. Toxicity is commonly seen when diazepam plus nordiazepam concentrations exceed 3,000 ng/mL. Adverse effects of benzodiazepines in therapeutic doses usually reflect the drug's pharmacology and include sedation, slurred speech, and ataxia. Respiratory depression/arrest may occur with large overdoses or following rapid IV injection with short-acting benzodiazepines.

**Reference Values:**
Therapeutic concentrations
Diazepam and Nordiazepam: 200-2,500 ng/mL

**Clinical References:**
2. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, Edited by CA Burtis, ER Ashwood, DE Bruns, WB Saunders Company, Philadelphia, PA, 2011, Table 60.2, pp 1109-1188

Digitoxin, Serum/Plasma

**Reference Values:**
Reporting limit determined each analysis

Digitoxin
Therapeutic Range: 10 - 30 ng/mL

**Clinical Information:** Digitoxin, a widely prescribed cardiac drug, has a narrow therapeutic window (a very small difference exists between therapeutic and toxic tissue concentrations). While excess digoxin can have serious side effects (e.g., cardiac dysrhythmias, heart failure, seizures, death), it is one of the few therapeutic drugs for which antidotal therapy is available. In toxic situations, antibody fragment therapy, which involves the administration of antibodies to digoxin (e.g., Digibind, Digoxin Immune Fab), is indicated. In manufacturing of Digibind, papain cleaves digoxin-specific IgG antibody into 2 antigen binding-site fragments (Fab fragments). These fragments bind to digoxin, block the active site of the digoxin molecule, and make it unavailable to its receptor molecule and biologically inactive. The Fab fragment-digoxin complex is then excreted by the kidney. Total digoxin concentration in blood increases approximately 10 to 30 fold after administration of Fab fragments. On the other hand, the unbound (free)
fraction, which is responsible for its pharmacological activity, decreases. Traditional digoxin assays performed by immunoassay (eg, DIG / Digoxin, Serum) measure both Fab fragment-bound (inactive) digoxin and free (active) digoxin (ie, total digoxin), and are unsuitable for managing patients when digoxin-specific Fab fragment therapy has been administered. Assays that only measure free digoxin levels are necessary in such situations. The kidneys provide the main route of Fab fragment elimination from the body. In patients with normal renal function, digoxin-specific Fab fragments are excreted in the urine with a biological half-life of 15 to 20 hours. Ordinarily, improvement in signs or symptoms of digoxin intoxication begins within a half hour or less after initiation of Fab fragment therapy. Clearance may be delayed in patients with renal failure. In such patients, toxicity may recur if previously bound drug is released from the Fab fragments, resulting in increased levels of free digoxin. Digoxin-like immunoreactive factors (DLIFs) are endogenous substances that can cross-react with testing antibodies used in some digoxin immunoassays, causing erroneous results. DLIFs may be seen in certain volume-expanded patients such as neonates, patients with renal or liver disease, and in women in the third trimester of pregnancy being treated with digoxin.(2) DLIFs are strongly bound to proteins and, in this assay, are removed prior to testing. The following ordering guidelines are offered: -When creatinine clearance is less than 30 mL/min/surface area: order free digoxin levels daily for 12 days (or until dismissal) -When creatinine clearance is equal to or above 30 mL/min/surface area (and the patient is not on renal-replacement therapy): order free levels daily for 72 hours, as long as the last level is not supratherapeutic (these patients are expected to have good clearance and a lower risk for reintoxication) -Also order total digoxin levels every other day during the time periods above, with a goal of determining whether there is correlation between changes in free and total levels.

**Useful For:** Evaluating recrudescent (breakthrough) digoxin toxicity in renal-failure patients
Assessing the need for more antidigoxin Fab to be administered Deciding when to reintroduce digoxin therapy Monitoring patients with possible digoxin-like immunoreactive factors (DLIFs)

**Interpretation:** The target therapeutic level is 0.4 to 0.9 ng/mL. Toxicity may be seen when free digoxin concentrations are 3.0 ng/mL or higher. Pediatric patients may tolerate higher concentrations. Therapeutic concentrations for free digoxin are 25% lower than therapeutic values for total digoxin due to the separation of protein-bound digoxin in the assay.

**Reference Values:**

<16 years:
Therapeutic ranges have not been established for patients who are under 16 years of age. In adults, the suggested serum free digoxin therapeutic range is 0.4-0.9 ng/mL.
 Toxic concentration: > or =3.0

> or =16 years:
0.4-0.9 ng/mL
Toxic concentration: > or =3.0 ng/mL

and various disturbances of cardiac rhythm. Digoxin improves the strength of myocardial contraction and results in the beneficial effects of increased cardiac output, decreased heart size, decreased venous pressure, and decreased blood volume. Digoxin therapy also results in stabilized and slowed ventricular pulse rate. These therapeutic effects are produced through a network of direct and indirect interactions upon the myocardium, blood vessels, and the autonomic nervous system. Digoxin is well absorbed after oral administration and is widely distributed to tissues, especially the heart, kidney, and liver. A number of factors can alter normal absorption, distribution, and bioavailability of the drug, including naturally occurring enteric bacteria in the bowel, presence of food in the gut, strenuous physical activity, ingestion of quinine or quinidine, and concomitant use of a wide range of drugs. Children generally require higher concentrations of digoxin. After oral administration, there is an early rise in serum concentration. Equilibration of serum and tissue levels occurs at approximately 6 to 8 hours. For this reason, blood specimens for digoxin analysis should be drawn at least 6 to 8 hours after drug administration. Digoxin is excreted primarily in the urine. The average elimination half-life is 36 to 40 hours, but may be considerably prolonged in those with renal disease, causing digoxin accumulation and toxicity. Symptoms of digoxin toxicity often mimic the cardiac arrhythmia’s for which the drug was originally prescribed (eg, heart block and heart failure). Other typical symptoms of toxicity include gastrointestinal effects, including anorexia, nausea, vomiting, abdominal pain and diarrhea, and neuropsychologic symptoms, such as fatigue, malaise, dizziness, cloudy or blurred vision, visual and auditory hallucination, paranoid ideation, and depression. Toxicity of digoxin may reflect several factors: the drug has a narrow therapeutic window (a very small difference exists between therapeutic and toxic tissue levels); individuals vary in their ability to metabolize and respond to digoxin; absorption of various oral forms of digoxin may vary over a 2-fold range; susceptibility to digitalis toxicity apparently increases with age.

**Useful For:** Monitoring digoxin therapy

**Interpretation:** The therapeutic range is 0.6 to 1.2 ng/mL. Levels of 4.0 ng/mL and above may be potentially life-threatening.

**Reference Values:**

<16 years:
Therapeutic ranges have not been established for patients who are less than 16 years of age.

> or =16 years:
Therapeutic range: 0.6-1.2 ng/mL
Toxic concentration: > or =4.0 ng/mL

**Clinical References:**

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**DPYDG**

**Dihydropyrimidine Dehydrogenase (DPYD) Full Gene Sequencing**

**Clinical Information:** 5-Fluorouracil (5-FU) and its orally administered prodrug, capecitabine, are fluoropyrimidine-based chemotherapeutic agents that are widely used for the treatment of colorectal cancer and other solid tumors. The dihydropyrimidine dehydrogenase (DPYD) gene encodes the rate-limiting enzyme for fluoropyrimidine catabolism and eliminates over 80% of administered 5-FU. Dihydropyrimidine dehydrogenase (DPYD) activity is subject to wide variability, mainly due to genetic variation (table 1). This results in a broad range of enzymatic deficiency from partial (3%-5% of population) to complete loss (0.2% of population) of enzyme activity.(2,3) Patients who are deficient in DPYD are at an increased risk for side effects and toxicity when undergoing 5-FU treatment.(4) In
addition, pathogenic homozygous or compound heterozygous variants within DPYD are associated with dihydropyrimidine dehydrogenase (DPD) deficiency. DPD deficiency shows large phenotypic variability, ranging from no symptoms to a convulsive disorder with motor and mental retardation. Table 1. Known Genetic Variations Associated with Fluoropyrimidine Treatment

| Gene cDNA numbering Alternative Name Enzyme Activity Phenotype ● | DPYD No variations identified *1 c.1905+1G->A *2A No activity or significantly reduced activity High risk for fluoropyrimidine toxicity c.1679T->G *13 c.1898delC *3 c.299_302delTCAT *7 c.1156G->T *12 c.2846A->T rs67376798 Reduced activity Increased risk for fluoropyrimidine toxicity c.1129-5923C->G rs75017182 c.703C->T *8 Probable reduced function Increased risk for fluoropyrimidine toxicity c.2983G->T *10 c.1003G->T *11 c.557A>G rs115232898 c.1601C>T *4 Normal activity **Normal risk for fluoropyrimidine toxicity c.1627A>G *5 c.2194C>T *6 c.85T->C *9A *Other or novel variations, besides those listed here, may also impact dihydropyrimidine-related side effects and tumor response and will be reported if detected. **Alleles that are categorized as having normal enzyme activity (eg, *4, *5, *6, *9A) will not be reported if detected because variants with normal enzyme activity are not expected to impact fluoropyrimidine-related side effects and tumor response. The DPYD gene is located on chromosome 1 and contains 2 transcripts. The longer transcript (NM_000110.3) contains 23 exons, and the shorter transcript (NM_00160301.1) contains 6 exons, with exon 6 being unique to this transcript. All exons from the longer transcript (NM_000110.3) and exon-intron boundaries are assessed. Genetic variations involved in the metabolic pathway of fluoropyrimidines have been shown to contribute to the differences in clinical outcomes including toxicity and tumor response.

**Useful For:** Identifying individuals at increased risk of toxicity when considering 5-fluorouracil (5-FU) and capecitabine chemotherapy treatment For an individual with suspected dihydropyrimidine dehydrogenase (DPD) deficiency, this test may be useful in identifying variants associated with decreased or absent DPD enzyme activity

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics recommendations as a guideline.(5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomics Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.


**DPYDV 65489**
Dihydropyrimidine Dehydrogenase (DPYD) Genotype

**Clinical Information:** 5-Fluorouracil (5-FU) and its orally administered prodrug, capecitabine, are fluoropyrimidine-based chemotherapeutic agents that are widely used for the treatment of colorectal cancer and other solid tumors. The dihydropyrimidine dehydrogenase (DPYD) gene encodes the rate-limiting enzyme for fluoropyrimidine catabolism and eliminates over 80% of administered 5-FU.
Dihydropyrimidine dehydrogenase (DPYD) activity is subject to wide variability, mainly due to genetic variation. This results in a broad range of enzymatic deficiency from partial (3%-5% of population) to complete loss (0.2% of population) of enzyme activity.(2,3) Patients who are deficient in DPYD are at an increased risk for side effects and toxicity when undergoing 5-FU treatment.(4) In addition, pathogenic homozygous or compound heterozygous variants within DPYD are associated with dihydropyrimidine dehydrogenase (DPD) deficiency. DPD deficiency shows large phenotypic variability, ranging from no symptoms to a convulsive disorder with motor and mental retardation. The following table displays the DPYD variants detected by this assay, the corresponding star allele, and the effect on DPYD enzyme activity. Other or novel variations, besides those listed here, may also impact fluoropyrimidine-related side effects and tumor response. DPYD Allele cDNA Nucleotide Change Effect on Enzyme Activity *1 None (wild type) Normal activity *2A 1905+1G->A No activity *7 299_302delTCAT No activity *8 703C->T Probable reduced activity *9B 2657G->A Variant of unknown significance *10 2983G->T Probable reduced activity *11 1003G->T Probable reduced activity *13 1679T->G No activity rs67376798 2846A->T Reduced activity rs75017182 1129-5923C->G Reduced activity rs11523289 557A->G Probable reduced activity

Useful For: Identifying individuals with genetic variants in DPYD who are at increased risk of toxicity when prescribed 5-fluorouracil (5-FU) or capecitabine chemotherapy treatment

Interpretation: An interpretive report will be provided. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomics Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
An interpretive report will be provided.


DHRF 62766 Dihydrorhodamine (DHR) Flow Cytometric N-Formyl-Methionyl-Leucyl-Phenylalanine (fMLP) Test, Blood

Clinical Information: This assay can be used for the diagnostic evaluation of Rac2 deficiency, which is a neutrophil defect that causes profound neutrophil dysfunction with decreased chemotaxis, polarization, superoxide anion production, azurophilic granule secretion. This disease is caused by inhibitory mutations in the RAC2 gene, which encodes a Rho family GTPase essential to neutrophil activation and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase function.(1) Patients with Rac2 deficiency have been shown to have normal neutrophil oxidative burst when stimulated with phorbol myristate acetate (PMA), indicating normal NADPH oxidase activity, but abnormal neutrophil responses to N-formyl-methionyl-leucyl-phenylalanine (fMLP), which is a physiological activator of neutrophils. The defective oxidative burst to fMLP, but not to PMA, indicates a signaling defect in Rac2 deficiency.(2)

Useful For: Diagnosis of Rac2 deficiency

Interpretation: An interpretive report will be provided, in addition to the quantitative values described in Clinical Information. Interpretation of the results of the quantitative dihydrorhodamine (DHR) flow cytometric assay has to include both the proportion of positive neutrophils for DHR after...
N-formyl-methionyl-leucyl-phenylalanine stimulation, and the mean fluorescence intensity.

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**Clinical References:**

**Dihydrorhodamine (DHR) Flow Cytometric Phorbol Myristate Acetate (PMA) Test, Blood**

**Clinical Information:** Chronic granulomatous disease (CGD) is caused by genetic defects in the gene components that encode the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme complex. These defects result in an inability to produce superoxide anions required for killing of bacterial and fungal organisms. Other clinical features include a predisposition to systemic granulomatous complications and autoimmunity.(1) There are 5 known genetic defects associated with the clinical phenotype of CGD.(2) The gene defects include mutations in the CYBB gene, encoding the gp91phox protein, which is X-linked and accounts for approximately 70% of CGD cases. Other gene defects are autosomal recessive: NCF1 (p47phox), NCF2 (p67phox), CYBA (p22phox), and NCF4 (p40phox). Typically, patients with X-linked CGD have the most severe disease, while patients with p47phox defects tend to have the best outcomes. Mutations in NCF4 encoding the p40phox protein has been the most recently described(3) and appears to be associated with more gastrointestinal disease with fewer infections. There is significant clinical variability even among individuals with similar mutations, in terms of NADPH oxidase function, indicating that there can be several modulating factors including the genetic defect, infection history, and granulomatous and autoimmune complications. There appears to be a correlation between very low NADPH superoxide production and worse outcomes. CGD can be treated with hematopoietic cell transplantation (HCT), which can be effective for the inflammatory and autoimmune manifestations. It has been shown that survival of patients with CGD was strongly associated with residual reactive oxygen intermediate (ROI) production, independent of the specific gene defect.(4) Measurement of NADPH oxidase activity through the dihydrorhodamine (DHR) flow cytometry assay contributed to the assessment of ROI. The diagnostic laboratory assessment for CGD includes evaluation of NADPH oxidase function in neutrophils, using either the nitroblue tetrazolium test (NBT) or the more analytically sensitive DHR test, as described here. Activation of neutrophils with phorbol myristate acetate (PMA) results in oxidation of DHR to a fluorescent compound, rhodamine 123, which can be measured by flow cytometry. Flow cytometry can distinguish between the different genetic forms of CGD.(5, 6) Complete myeloperoxidase (MPO) deficiency can cause a false-positive result for CGD in the DHR flow cytometric assay (7); however, there is a difference between the percent DHR+ neutrophils and the mean fluorescence intensity (MFI) after PMA stimulation that allows discrimination between true X-linked CGD and complete MPO deficiency. Further, the addition of recombinant human MPO enhances the DHR signal in MPO-deficient neutrophils but not in CGD neutrophils.(7) It is important to have quantitative measures in the DHR flow cytometry assay to effectively use the test for diagnosis of the different forms of CGD as well as for monitoring chimerism and NADPH oxidase activity post-HCT. These quantitative measures include assessment of the relative proportion (%) of neutrophils that are positive for DHR fluorescence after PMA stimulation and the relative fluorescence intensity of DHR (MFI) on neutrophils after activation. Female carriers of
X-linked CGD can become symptomatic for CGD due to skewed lyonization (X chromosome inactivation).(8) Age-related acquired skewing of lyonization can also cause increased susceptibility to infections in carriers of X-linked CGD.(9) While germline mutations are more common in CGD, there have been reports of de novo, sporadic mutations in the CYBB gene, causing X-linked CGD in male patients whose mothers are not carriers for the affected allele. Additionally, somatic mosaicism has been reported in patients with X-linked CGD who have small populations of normal cells.(10) There are also reports of triple somatic mosaicism in female carriers (11,12) as well as late-onset disease in an adult female who was a somatic mosaic for a novel mutation in the CYBB gene.(13) Therefore, the clinical, genetic, and age spectrum of CGD is varied and laboratory assessment of NADPH oxidase activity after neutrophil stimulation, coupled with appropriate interpretation, is critical to achieving an accurate diagnosis or for monitoring patients posttransplant.

**Useful For:** Diagnosis of chronic granulomatous disease (CGD), X-linked and autosomal recessive forms, complete myeloperoxidase (MPO) deficiency; monitoring chimerism and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase function posthematopoietic cell transplantation Assessing residual NADPH oxidase activity pretransplant Identification of carrier females for X-linked CGD; assessment of changes in Lyonization with age in carrier females

**Interpretation:** An interpretive report will be provided, in addition to the quantitative values described in Clinical Information. Interpretation of the results of the quantitative dihydrorhodamine (DHR) flow cytometric assay has to include both the proportion of positive neutrophils for DHR after phorbol myristate acetate stimulation, and the mean fluorescence intensity. Additionally, visual assessment of the pattern of DHR fluorescence is helpful in discriminating between the various genetic defects associated with chronic granulomatous disease and complete myeloperoxidase deficiency.

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Dihydrorhodamine (DHR) Flow Cytometric Test, Blood

Clinical Information: Chronic granulomatous disease (CGD) is caused by genetic defects in the gene components that encode the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme complex. These defects result in an inability to produce superoxide anions required for killing bacterial and fungal organisms. Other clinical features include a predisposition to systemic granulomatous complications and autoimmunity.(1) There are 5 known genetic defects associated with the clinical phenotype of CGD.(2) The gene defects include mutations in the CYBB gene, encoding the gp91phox protein, which is X-linked and accounts for approximately 70% of CGD cases. Other gene defects are autosomal recessive: NCF1 (p47phox), NCF2 (p67phox), CYBA (p22phox), and NCF4 (p40phox). Typically, patients with X-linked CGD have the most severe disease, while patients with p47phox defects tend to have the best outcomes. Mutations in NCF4 encoding the p40phox protein have been the most recently described(3) and appears to be associated with more gastrointestinal disease with fewer infections. There is significant clinical variability even among individuals with similar mutations, in terms of NADPH oxidase function, indicating that there can be several modulating factors including the genetic defect, infection history, and granulomatous and autoimmune complications. There appears to be a correlation between very low NADPH superoxide production and worse outcomes. CGD can be treated with hematopoietic cell transplantation (HCT), which can be effective for the inflammatory and autoimmune manifestations. It has been shown that survival of patients with CGD was strongly associated with residual reactive oxygen intermediate (ROI) production, independent of the specific gene defect.(4) Measurement of NADPH oxidase activity through the dihydrorhodamine (DHR) flow cytometry assay contributed to the assessment of ROI. The diagnostic laboratory assessment for CGD includes evaluation of NADPH oxidase function in neutrophils, using either the nitroblue tetrazolium test (NBT) or the more analytically sensitive DHR test, as described here. Activation of neutrophils with phorbol myristate acetate (PMA) results in oxidation of DHR to a fluorescent compound, rhodamine 123, which can be measured by flow cytometry. Flow cytometry can distinguish between the different genetic forms of CGD.(5, 6) Complete myeloperoxidase (MPO) deficiency can cause a false-positive result for CGD in the DHR flow cytometric assay (7); however, there is a difference between the percent DHR+ neutrophils and the mean fluorescence intensity (MFI) after PMA stimulation that allows discrimination between true X-linked CGD and complete MPO deficiency. Further, the addition of recombinant human MPO enhances the DHR signal in MPO-deficient neutrophils but not in CGD neutrophils. (7) It is important to have quantitative measures in the DHR flow cytometry assay to effectively use the test for diagnosis of the different forms of CGD as well as for monitoring chimism and NADPH oxidase activity post-HCT. These quantitative measures include assessment of the relative proportion (%) of neutrophils that are positive for DHR fluorescence after PMA stimulation and the relative fluorescence intensity of DHR (MFI) on neutrophils after activation. This assay can also be used for the diagnostic evaluation of Rac2 deficiency, which is a neutrophil defect that causes profound neutrophil dysfunction with decreased chemotaxis, polarization, superoxide anion production, azurophilic granule secretion. This disease is caused by inhibitory mutations in the RAC2 gene, which encodes a Rho family GTPase essential to neutrophil activation and NADPH oxidase function.(8) Patients with Rac2 deficiency have been shown to have normal neutrophil oxidative burst when stimulated with PMA, indicating normal NADPH oxidase activity, but abnormal neutrophil responses to N-formyl-methionyl-leucyl-phenylalanine (fMLP), which is a physiological activator of neutrophils. The defective oxidative burst to fMLP, but not to PMA, indicates a signaling defect in Rac2 deficiency.(9) Female carriers of X-linked CGD can become symptomatic for CGD due to skewed lyonization (X chromosome inactivation).(10) Age-related acquired skewing of lyonization can also cause increased susceptibility to infections in carriers of X-linked CGD.(11) While germline mutations are more common in CGD, there have been reports of de novo, sporadic mutations in the CYBB gene, causing X-linked CGD in male patients whose mothers are not carriers for the affected allele. Additionally, somatic mosaicism has been reported in patients with X-linked CGD who have small populations of normal cells.(12) There are also reports of triple somatic mosaicism in female carriers (13,14) as well as late-onset disease in an adult female who was a somatic mosaic for a novel mutation in the CYBB gene.(15) Therefore, the clinical, genetic, and age spectrum of CGD is varied and laboratory assessment of NADPH oxidase activity after neutrophil stimulation, coupled with appropriate interpretation, is critical to achieving an accurate diagnosis or for monitoring patients posttransplant.
Useful For: Diagnosis of chronic granulomatous disease (CGD), X-linked and autosomal recessive forms, Rac2 deficiency, complete myeloperoxidase (MPO) deficiency; monitoring chimerism and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase function post hematopoietic cell transplantation; Assessing residual NADPH oxidase activity pretransplant; Identification of carrier females for X-linked CGD; assessment of changes in lyonization with age in carrier females.

Interpretation: An interpretive report will be provided, in addition to the quantitative values. Interpretation of the results of the quantitative dihydrorhodamine (DHR) flow cytometric assay has to include both the proportion of positive neutrophils for DHR after phorbol myristate acetate (PMA) and/or N-formyl-methionyl-leucyl-phenylalanine (fMLP) stimulation, and the mean fluorescence intensity (MFI). Additionally, visual assessment of the pattern of DHR fluorescence is helpful in discriminating between the various genetic defects associated with chronic granulomatous disease (CGD) and complete myeloperoxidase (MPO) deficiency.

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<td>Control MFI fMLP ox-DHR+</td>
<td>MFI</td>
<td>&gt; or =2 The appropriate age-related reference values for Absolute Neutrophil Count will be provided on the report.</td>
</tr>
</tbody>
</table>

Dihydrotestosterone, Serum

Clinical Information: The principal prostatic androgen is dihydrotestosterone (DHT). Levels of DHT remain normal with aging, despite a decrease in the plasma testosterone, and are not elevated in benign prostatic hyperplasia (BPH). (1) DHT is generated by reduction of testosterone by 5 alpha-reductase. Two isoenzymes of 5 alpha-reductase have been discovered. Type 1 is present in most tissues in the body where 5 alpha-reductase is expressed, and is the dominant form in sebaceous glands. Type 2 is the dominant isoenzyme in genital tissues, including the prostate. Androgenetic alopecia (AGA; male-pattern baldness) is a hereditary and androgen-dependent progressive thinning of the scalp hair that follows a defined pattern. (2) While the genetic involvement is pronounced but poorly understood, major advances have been achieved in understanding the principal elements of androgen metabolism that are involved. DHT may be related to baldness. High concentrations of 5 alpha-reductase have been found in frontal scalp and genital skin and androgen-dependent processes are predominantly due to the binding of DHT to the androgen receptor (AR). Since the clinical success of treatment of AGA with modulators of androgen metabolism or hair growth promoters is limited, sustained microscopic follicular inflammation with connective tissue remodeling, eventually resulting in permanent hair loss, is considered a possible cofactor in the complex etiology of AGA. Currently available AGA treatment modalities with proven efficacy are oral finasteride, a competitive inhibitor of 5 alpha-reductase type 2, and topical minoxidil, an adenosine triphosphate-sensitive potassium channel opener that has been reported to stimulate the production of vascular endothelial growth factor in cultured dermal papilla cells. Currently, many patients with prostate disease receive treatment with a 5 alpha-reductase inhibitor such as finasteride (Proscar) to diminish conversion of DHT from testosterone. See Steroid Pathways in Special Instructions.

Useful For: Monitoring patients receiving 5 alpha-reductase inhibitor therapy or chemotherapy Evaluating patients with possible 5 alpha-reductase deficiency

Interpretation: Patients taking 5 alpha-reductase inhibitor have decreased dihydrotestosterone (DHT) serum levels. Patients with genetic 5 alpha-reductase deficiency (a rare disease) also have reduced DHT serum levels. DHT should serve as the primary marker of peripheral androgen production. However, because it is metabolized rapidly and has a very high affinity for sex hormone-binding globulin (SHBG), DHT does not reflect peripheral androgen action. Instead, its distal metabolite, 3 alpha, 17 beta-androstanediol glucuronide, serves as a better marker of peripheral androgen action. See Steroid Pathways in Special Instructions.

Reference Values:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mean Age</th>
<th>Reference Range (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (&gt;6 months and prepubertal)</td>
<td>7.1 years</td>
<td>&lt; or =50</td>
</tr>
<tr>
<td>II</td>
<td>12.1 years</td>
<td>&lt; or =200</td>
</tr>
<tr>
<td>III</td>
<td>13.6 years</td>
<td>80-330</td>
</tr>
<tr>
<td>IV</td>
<td>15.1 years</td>
<td>220-520</td>
</tr>
<tr>
<td>V</td>
<td>18 years</td>
<td>240-650 18 years: 112-955 pg/mL Females Cord blood: &lt; or =50 pg/mL &lt; or =6 months: &lt; or =1,200 pg/mL Tanner Stages</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mean Age</th>
<th>Reference Range (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (&gt;6 months and prepubertal)</td>
<td>7.1 years</td>
<td>&lt; or =50</td>
</tr>
<tr>
<td>II</td>
<td>10.5 years</td>
<td>&lt; or =300</td>
</tr>
<tr>
<td>III</td>
<td>11.6 years</td>
<td>&lt; or =300</td>
</tr>
<tr>
<td>IV</td>
<td>12.3 years</td>
<td>&lt; or =300</td>
</tr>
</tbody>
</table>
Clinical References:

Dilated Cardiomyopathy Multi-Gene Panel, Blood

Clinical Information: The cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathy can be caused by inherited, genetic factors, or by nongenetic (acquired) causes such as infection or trauma. When the presence or severity of the cardiomyopathy observed in a patient cannot be explained by acquired causes, genetic testing for the inherited forms of cardiomyopathy may be considered. Overall, the cardiomyopathies are some of the most common genetic disorders. The inherited forms of cardiomyopathy include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and left ventricular noncompaction (LVNC). DCM is established by the presence of left ventricular enlargement and systolic dysfunction. DCM may present with heart failure with symptoms of congestion, arrhythmias, and conduction system disease, or thromboembolic disease (stroke). The most recent estimates of the incidence of DCM suggest that the condition affects approximately 1 in every 250 people. These estimates are higher than originally reported due to subclinical phenotypes and underdiagnosis. After exclusion of nongenetic causes such as ischemic injury, DCM is traditionally referred to as "idiopathic" dilated cardiomyopathy. Approximately 20% to 50% of individuals with idiopathic DCM may have an identifiable genetic cause for their disease. Families with 2 or more affected individuals are diagnosed with familial dilated cardiomyopathy. The majority of familial dilated cardiomyopathy is inherited in an autosomal dominant manner; however, autosomal recessive and X-linked forms have also been reported. At least 28 genes have been reported in association with DCM, including genes encoding the cardiac sarcomere and other proteins involved in proteins responsible for cardiac muscle contraction. Some genes associated with DCM also cause other forms of hereditary cardiomyopathy, cardiac channelopathies, skeletal myopathies, or metabolic defects. See table for details regarding the genes tested by this panel and associated diseases. Genes included in the Dilated Cardiomyopathy Multi-Gene Panel Gene Protein Inheritance Disease Association ABCC9 ATP-Binding cassette, subfamily C, member 9 AD DCM, Cantu syndrome ACTC1 Actin, alpha, cardiac muscle AD CHD, DCM, HCM, LVNC ACTN2 Actinin, alpha-2 AD DCM, HCM, DCM ANKRD1 Ankyrin repeat domain-containing protein 1 AD HCM, DCM CRYAB Crystallin, alpha-B AD, AR DCM, myofibrillar myopathy CSRP3 Cysteine-and glycine-rich protein 3 AD DCM, DCM, HCM ARVC, myofibrillar myopathy, RCM with AV block, neurogenic scapuloperoneal syndrome Kaeser type, LGMD LAMA4 Laminin, alpha-4 AD DCM LAMP2 Lysosome-associated membrane protein 2 X-linked Danon disease LDB3 LIM domain-binding 3 AD DCM, LVNC, myofibrillar myopathy LMNA Lamin A/C AD, AR DCM, EMD, LGMD, congenital muscular dystrophy (see OMIM for full listing) MYBPC3 Myosin-binding protein-C, cardiac AD HCM, DCM MYH6 Myosin, heavy chain 6, cardiac muscle, alpha HCM, DCM MYH7 Myosin, heavy chain 7, cardiac muscle, beta AD HCM, DCM, LVNC, myopathy MYOTP Myopalladin AD HCM, DCM NEXN Nexilin AD HCM, DCM
Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hereditary dilated cardiomyopathy (DCM) Establishing a diagnosis of a hereditary DCM, and in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying a pathogenic variant within a gene known to be associated with disease features that allows for predictive testing of at-risk family members

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values: An interpretive report will be provided.


Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and...
wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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</thead>
<tbody>
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<td>0</td>
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<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


---

**FDILT**

**Diltiazem (Cardizem, Dilacor)**

**Reference Values:**

Reference Range: 50 - 200 ng/mL

---

**CDRVT**

**Dilute Russell Viper Venom Time (DRVVT) Confirmation Ratio**

**Reference Values:**

Only orderable as part of a profile. For more information see DRVTI / Dilute Russell Viper Venom Time (DRVVT), with Reflex, Plasma and DRVTJ / Dilute Russell Viper Venom Time (DRVVT) Mix and Confirm Reflexes, Plasma.

<1.2

Normal ranges for children: Not clearly established, but similar to normal ranges for adults, except for newborn infants whose results may not reach adult values until 3 to 6 months of age.

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**DRVTK**

**Dilute Russell Viper Venom Time (DRVVT) Interpretation**

**Reference Values:**

Only orderable as a part of a reflex. For more information see DRVTI / Dilute Russell Viper Venom Time (DRVVT), with Reflex, Plasma.
**DRVTJ**

Dilute Russell Viper Venom Time (DRVVT) Mix and Confirm Reflexes, Plasma

**Reference Values:**
Only orderable as a part of a profile. For more information see DRVTI / Dilute Russell Viper Venom Time (DRVVT), with Reflex, Plasma.

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**MDRVT**

Dilute Russell Viper Venom Time (DRVVT) Mix Ratio

**Reference Values:**
Only orderable as part of a profile. For more information see DRVTI / Dilute Russell Viper Venom Time (DRVVT), with Reflex, Plasma and DRVTJ / Dilute Russell Viper Venom Time (DRVVT) Mix and Confirm Reflexes, Plasma.

<1.2

Normal ranges for children: Not clearly established, but similar to normal ranges for adults, except for newborn infants whose results may not reach adult values until 3 to 6 months of age.

---

**DRVTI**

Dilute Russell Viper Venom Time (DRVVT), with Reflex, Plasma

**Clinical Information:** Lupus anticoagulants (LA) are immunoglobulins (IgG, IgM, IgA, or a combination of these) of autoimmune type that are specifically directed against antigenic complexes of negatively charged phospholipids (such as phosphatidylserine or phosphatidylethanolamine) and coagulation-related proteins such as beta-2-glycoprotein I (beta-2-GPI) or clotting factors including prothrombin (factor II) or factor X, and cause prolongation of phospholipid-dependent clotting time tests due to inhibition. LA are functionally and clinically distinct members of a broader group of antiphospholipid autoantibodies (APA) that includes immunologically detectable anticardiolipin antibodies or antibodies against other phospholipid-protein complexes. LA interfere with specific coagulation factor-phospholipid interactions, typically causing prolongation of 1 or more phospholipid-dependent clotting time tests (eg, activated partial thromboplastin time: APTT, dilute Russell viper venom time: DRVVT) due to inhibition. This characteristic in vitro inhibition can be overcome by addition of excess phospholipid. Because of the heterogeneous nature of LA antibodies, no single coagulation test can identify or exclude all LA. Currently, the International Society on Thrombosis and Haemostasis and the Clinical and Laboratory Standards Institute (CLSI) recommend testing for LA with at least 2 phospholipid-dependent clotting time assays based on different coagulation pathways and principles (eg, lupus sensitive APTT and DRVVT) In addition, given the potential for false-positive results in patients on anticoagulants, a profile or panel of coagulation testing is recommended, including the prothrombin time (PT), APTT, thrombin time (TT), and the DRVVT. If the PT, APTT, or DRVVT are prolonged, additional testing may include mixing tests with normal plasma (to evaluate for inhibition) and the use of excess phospholipid in appropriate assay systems to evaluate for phospholipid-dependent inhibition. Additional reflexive testing helps determine the presence or absence of anticoagulants or inhibitors to other factors. The diagnosis of LA requires performance and interpretation of complex coagulation testing, as well as correlation with available clinical information, including evidence of persistence of LA over time (> or =12 weeks). The venom obtained from the Russell viper (Vipera russelli) contains enzymes that directly activate coagulation factors V and X, bypassing the activation of factors VII, VIII, IX, XI, and XII, and, therefore, the effect of deficiencies or inhibitors of these factors. Diluting the phospholipid necessary for the clotting factor interactions increases the sensitivity to LA and the likelihood of identifying a phospholipid-dependent inhibitor that may not be detected by other coagulation tests that have a higher phospholipid content (eg, LA-insensitive APTT reagents). The DRVVT screen ratio test is one of several available in vitro tests that may be used to screen and confirm the presence of LA or to help exclude LA. The DRVVT may be abnormally prolonged (DRVVT screen ratio > or =1.2) by LA as well as coagulation factor deficiencies, anticoagulant effects, or other types of coagulation factor inhibitors. Specimens with abnormal results (DRVVT screen ratio > or =1.2) are subjected to reflexive testing (DRVVT mix and confirmation.
ratios) as described in the Testing Algorithm (also see Interpretation). It is advisable to use the DRVVT screen, mix and confirm ratio results in conjunction with other appropriate coagulation tests (reflexive testing panels) to diagnose or exclude LA. Although LA cause prolonged clotting times in vitro, there is a strong association with thrombosis risk. However, not all patients with persisting LA develop thrombosis.

**Useful For:** Detecting and confirming or helping to exclude the presence of lupus anticoagulants (LA) Identifying LA that do not prolong the activated partial thromboplastin time (APTT) Evaluating unexplained prolongation of the APTT or prothrombin time clotting tests

**Interpretation:** Dilute Russell viper venom time (DRVVT) screen ratio (<1.2): A normal DRVVT screen ratio (<1.2) indicates that lupus anticoagulants (LA) is not present, or not detectable, by this method (but might be detected with other methods). Abnormal DRVVT screen ratio (DRVVT screen ratio > or =1.2) may suggest the presence of LA; however, other possibilities include: -Deficiencies or dysfunction of factors I (fibrinogen), II, V, or X, congenital or acquired. -Inhibitors of factor V, or occasionally by inhibitors of factor VIII, or other specific or nonspecific inhibitors -Anticoagulation therapy effects (see Cautions) Further evaluation consists of performing mixing studies with an equal volume of normal pooled plasma (DRVVT 1:1 mix) to investigate the possibility of coagulation factor deficiency (suggested by DRVVT mix ratio <1.2) and to evaluate inhibition (suggested by DRVVT mix ratio > or =1.2) and mixing patient plasma with DRVVT reagent enriched in phospholipid (DRVVT confirmatory reagent) (DRVVT mix and DRVVT confirm ratios). Possible combinations of results include the following: -DRVVT screen ratio > or =1.2 and DRVVT mix ratio <1.2 DRVVT confirm ratio <1.2: No evidence of LA. This data may reflect anticoagulation therapy effects or other (congenital or acquired) coagulopathy. -DRVVT screen ratio > or =1.2 and DRVVT mix ratio > or =1.2 DRVVT confirm ratio <1.2: The prolonged and inhibited DRVVT (DRVVT screen and mix ratios) may reflect presence of a specific factor inhibitor (eg, factor V inhibitor), anticoagulation therapy effects, or other nonspecific inhibitors as can be seen with monoclonal protein disorders, lymphoproliferative disease, etc. Although LA cannot be conclusively excluded, the DRVVT confirm ratio of <1.2 makes this less likely. -DRVVT screen ratio > or =1.2 and DRVVT mix ratio <1.2 DRVVT confirm ratio > or =1.2: Although mixing study of the prolonged DRVVT (DRVVT screen and mix ratios) provides no evidence of inhibition, additional phospholipid shortens the clotting time (DRVVT confirm ratio), suggesting presence of LA. -DRVVT screen ratio > or =1.2 and DRVVT mix ratio > or =1.2 DRVVT confirm ratio > or =1.2: The data are consistent with presence of LA, provided anticoagulant effect can be excluded (see Cautions). Because no single coagulation test can identify or exclude all LAs, and because of the complexity of testing LA, a combination or panel of coagulation tests is recommended: LUPPR / Lupus Anticoagulant Profile THRMP / Thrombophilia Profile PROCT / Prolonged Clot Time Profile DRVVT assays ordered as a single, stand-alone test should be interpreted within patient clinical context and close attention to medication use by patient (see Cautions).

**Reference Values:**
Dilute Russell viper venom time screen ratio <1.2

Normal ranges for children: Not clearly established, but similar to normal ranges for adults, except for newborn infants whose results may not reach adult values until 3 to 6 months of age.

**Diptheria Toxoid IgG Antibody, Serum**

**Clinical Information:** Diptheria is an acute, contagious, febrile illness caused by the bacterium Corynebacterium diphtheriae. The disease is classically characterized by a combination of localized inflammation in the upper respiratory tract with the formation of a diphtheric pseudomembrane over the oropharynx, including the tonsils, pharynx, larynx and posterior nasal passages. Corynebacterium diphtheriae produces a potent diptheria exotoxin that is absorbed systemically and can lead to cardiac failure and paralysis of the diaphragm. The disease is preventable by vaccination with diptheria toxoid, which stimulates antitoxin antibodies. In the United States, diphteria toxoid is administered to children as part of the combined diphtheria, tetanus, and acellular pertussis (TDaP) vaccine. A patient's immunological response to diphteria toxoid vaccination can be determined by measuring antitoxin IgG antibody using this enzyme immunoassay technique. An absence of antibody formation postvaccination may relate to immune deficiency disorders, either congenital or acquired, or iatrogenic due to immunosuppressive drugs.

**Useful For:** Determining a patient's immunological response to diphteria toxoid vaccination

**Aids in the evaluation of immunodeficiency**

**Interpretation:** Results $\geq 0.01$ IU/mL suggest a vaccine response. A diphtheria toxoid booster should be considered for patients with antitoxin IgG values between 0.01 and less than 0.1 IU/mL.

**Reference Values:**
- Vaccinated: Positive ($>0.01$ IU/mL)
- Unvaccinated: Negative ($<0.01$ IU/mL)
- Reference Values apply to all ages.

**Clinical References:**

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**Diphtheria/Tetanus Antibody Panel, Serum**

**Clinical Information:** Diphteria is an acute, contagious, febrile illness caused by the bacterium Corynebacterium diphtheriae. The disease is classically characterized by a combination of localized inflammation in the upper respiratory tract with the formation of a diphtheric pseudomembrane over the oropharynx, including the tonsils, pharynx, larynx and posterior nasal passages. Corynebacterium diphtheriae produces a potent diphteria exotoxin that is absorbed systemically and can lead to cardiac failure and paralysis of the diaphragm. The disease is preventable by vaccination with diphteria toxoid, which stimulates antitoxin antibodies. In the United States, diphteria toxoid is administered to children as part of the combined diphtheria, tetanus, and acellular pertussis (TDaP) vaccine. A patient's immunological response to diphteria toxoid vaccination can be determined by measuring antitoxin IgG antibody using this enzyme immunoassay technique. An absence of antibody formation postvaccination may relate to immune deficiency disorders, either congenital or acquired, or iatrogenic due to immunosuppressive drugs. Tetanus results from contamination of wounds or lacerations with Clostridium tetani spores from the environment. The spores germinate to actively replicating bacterial cells localized within the wound and produce the heat-labile toxin, tetanospsamin. Tetanospsamin attaches to peripheral nerve endings and travels to the central nervous system (CNS) where it blocks inhibitory impulses to motor neurons and leads to severe, spastic muscle contractions, a classic characteristic of tetanus. The disease is preventable by vaccination with tetanus toxoid (formaldehyde-treated tetanospsamin), which stimulates development of antitoxin antibodies. In the United States, tetanus toxoid is administered to children as part of the combined diphtheria, tetanus, acellular pertussis (TDaP) vaccine. Two to 3 weeks following vaccination, a patient's immunological response may be assessed by measuring the total antitoxin toxoid IgG antibody level in serum. An absence of antibody formation postvaccination may relate to immune deficiency disorders,
either congenital or acquired, or iatrogenic due to immunosuppressive drugs.

**Useful For:** Assessment of an antibody response to tetanus and diphtheria toxoid vaccines, which should be performed at least 3 weeks after immunization. Aids in the evaluation of immunodeficiency.

**Interpretation:** Diphtheria: Results $> 0.01$ IU/mL suggest a vaccine response. A diphtheria toxoid booster should be considered for patients with antidiphtheria toxoid IgG values between 0.01 and less than 0.1 IU/mL. Tetanus: Results $> 0.01$ IU/mL suggest a vaccine response. A tetanus toxoid booster should strongly be considered for patients with antitetanus toxoid IgG values between 0.01 and 0.5 IU/mL. Some cases of tetanus, usually mild, have occasionally been observed in patients who have a measurable serum level of 0.01 to 1.0 IU/mL.

**Reference Values:**

**DIPHtheria TOXOID IgG Antibody**
- Vaccinated: Positive ($> 0.01$ IU/mL)
- Unvaccinated: Negative ($< 0.01$ IU/mL)
- Reference values apply to all ages.

**TETANUS TOXOID IgG Antibody**
- Vaccinated: Positive ($> 0.01$ IU/mL)
- Unvaccinated: Negative ($< 0.01$ IU/mL)
- Reference values apply to all ages.

**Clinical References:**

**FDIPY**

**Dipiridamole, Serum/Plasma**

**Reference Values:** Reporting limit determined each analysis

Surname(s): Persantine

Steady-state trough plasma concentrations following a three times daily regimen of:
- 50 mg: 0.1 - 1.5 mcg/mL
- 75 mg: 0.1 - 2.6 mcg/mL

**DCTR**

**Direct Antiglobulin Test (Polyspecific), Blood**

**Clinical Information:** IgG antibody or complement components secondary to the action of IgM antibody may be present on the patient's own RBCs or on transfused RBCs.

**Useful For:** Demonstrating in vivo coating of RBCs with IgG or the complement component C3d in the following settings: -Autoimmune hemolytic anemia -Hemolytic transfusion reactions -Drug-induced hemolytic anemia

**Interpretation:** Negative: No IgG antibody or complement (C3d) detected on the surface of the red cell. Positive: Test DATR will be ordered and performed.
Reference Values:
Negative
If positive, test DATR will be performed.


FDSAC 91414

Disaccharidase Analysis

Reference Values:
Lactase: Range 24.5 +/- 8.0
Abnormal <15.0

Units = uM/min/gram protein

Sucrase: Range 54.4 +/- 25.4
Abnormal <25.0

Units = uM/min/gram protein

Maltase: Range 160.8 +/- 62.8
Abnormal <100.0

Units = uM/min/gram protein

Palatinase: Range 11.1 +/- 6.5
Abnormal <5.0

Units = uM/min/gram protein

FDISP 91595

Disaccharidase Panel

Reference Values:

<table>
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<tr>
<th></th>
<th>3%ile</th>
<th>10%ile</th>
<th>mean</th>
<th>s.d.</th>
<th>n</th>
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</thead>
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<td>17.0</td>
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<td>Maltase</td>
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<td>120.0</td>
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<tr>
<td>Palatinase</td>
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<td>27.4</td>
<td>48.7</td>
<td>18.2</td>
<td>66</td>
</tr>
</tbody>
</table>

Units=umoles/min/gram protein data from normal patients
Interpretation added.

G097 65580

Distal Myopathy Panel (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

G100 65581

Distal Weakness Expanded Panel (Bill Only)
**FDIRU 57280**

**Diuretic Screen, Urine**

**Reference Values:**
Qualitative diuretic screen includes: benzthiazide, bumetanide, chlorothiazide, chlorthalidone, furosemide, hydrochlorothiazide, hydroflumethiazide, and metolazone.

**FDM1 91592**

**DMPK DNA Test (DM1)**

**Clinical Information:** Detects CTG repeat expansions in the muscle protein kinase (DMPK) gene. Typical presentation: Adults may present with a range of symptoms from cataracts to significant muscle wasting, cardiac complications, ptosis and myotonia, infants may present with severe hypotonia, skeletal deformities, developmental delay and mental retardation.

**Reference Values:**
A final report will be attached in MayoAccess.

**CRITH 62925**

**DNA Double-Stranded (dsDNA) Antibodies by Crithidia luciliae IFA, IgG, Serum**

**Reference Values:**
Only orderable as reflex. For more information see ADNAR / DNA Double-Stranded (dsDNA) Antibodies with Reflex, IgG, Serum.

**ADNAR 63073**

**DNA Double-Stranded (dsDNA) Antibodies with Reflex, IgG, Serum**

**Clinical Information:** Double-stranded (ds, native) DNA (dsDNA) antibodies of the IgG class are an accepted criterion (American College of Rheumatology) for the diagnosis of systemic lupus erythematosus (SLE).(1-3) dsDNA antibodies are detectable in approximately 85% of patients with untreated SLE, and are rarely detectable in other connective tissue diseases. Weakly positive results caused by low-avidity antibodies to dsDNA are not specific for SLE and can occur in a variety of diseases. Testing for IgG antibodies to dsDNA is indicated in patients who have a positive test for antinuclear antibodies (ANA) along with signs and symptoms that are compatible with the diagnosis of SLE.(2) If the ANA test is negative, there is no reason to test for antibodies to dsDNA.(2) The levels of IgG antibodies to dsDNA in serum are known to fluctuate with disease activity in lupus erythematosus, often increasing prior to an increase in inflammation and decreasing in response to therapy.(1,2) See Connective Tissue Diseases Cascade (CTDC) in Special Instructions.

**Useful For:** Evaluating patients with signs and symptoms consistent with systemic lupus erythematosus (SLE)

**Interpretation:** A positive test result for double-stranded DNA (dsDNA) antibodies is consistent with the diagnosis of systemic lupus erythematosus. A reference range study conducted at the Mayo Clinic demonstrated that, within a cohort of healthy adults (n=120), no individuals between the ages of 18 and 60 (n=78) had detectable anti-dsDNA antibodies. Above the age of 60 (n=42), 11.9% of individuals (n=5) had a borderline result for dsDNA antibodies and 4.8% of individuals (n=2) had a positive result.

**Reference Values:**
<30.0 IU/mL (negative)
30.0-75.0 IU/mL (borderline)
>75.0 IU/mL (positive)
Negative is considered normal.
Reference values apply to all ages.


DNA Double-Stranded (dsDNA) Antibodies, IgG, Serum

Clinical Information: Double-stranded (ds, native) DNA (dsDNA) antibodies of the IgG class are an accepted criterion (American College of Rheumatology) for the diagnosis of systemic lupus erythematosus (SLE). (1-3) dsDNA antibodies are detectable in approximately 85% of patients with untreated SLE, and are rarely detectable in other connective tissue diseases. Weakly-positive results caused by low-avidity antibodies to dsDNA are not specific for SLE and can occur in a variety of diseases. Testing for IgG antibodies to dsDNA is indicated in patients who have a positive test for antinuclear antibodies (ANA) along with signs and symptoms that are compatible with the diagnosis of SLE. If the ANA test is negative, there is no reason to test for antibodies to dsDNA. (2) The levels of IgG antibodies to dsDNA in serum are known to fluctuate with disease activity in lupus erythematosus, often increasing prior to an increase in inflammation and decreasing in response to therapy. (1,2)

Useful For: Evaluating patients with signs and symptoms consistent with systemic lupus erythematosus (SLE) Monitoring patients with documented SLE for flares in disease activity

Interpretation: A positive test result for double-stranded DNA (dsDNA) antibodies is consistent with the diagnosis of systemic lupus erythematosus. A reference range study conducted at the Mayo Clinic demonstrated that, within a cohort of healthy adults (n=120), no individuals between the ages of 18 and 60 (n=78) had detectable anti-dsDNA antibodies. Above the age of 60 (n=42), 11.9% of individuals (n=5) had a borderline result for dsDNA antibodies and 4.8% of individuals (n=2) had a positive result.

Reference Values:
<30.0 IU/mL (negative)
30.0-75.0 IU/mL (borderline)
>75.0 IU/mL (positive)
Negative is considered normal.
Reference values apply to all ages.


DNAJB9 Immunostain, Technical Component Only

Clinical Information: DNAJB9 (Dnaj (hsp40) homolog, subfamily b, member 9) is a cochaperone that is upregulated in response to endoplasmic reticulum (ER) stress and plays a role in protein folding or ER-associated protein degradation. Proteomic analysis using microdissection of glomeruli, protease digestion, and mass spectrometry indicates that the DNAJB9 protein is specifically identified in glomeruli of patients with fibrillary glomerulonephritis. (Mayo Clinic unpublished observations) By
immunohistochemistry there is an intense smudgy staining of extracellular glomerular deposits for DNAJB9 that is not present in glomeruli from healthy individuals, patients with amyloidosis, or patients with other glomerular diseases. The presence of DNAJB9, in the appropriate clinical and pathological context, can be helpful in diagnosis of this disease.

Useful For: Diagnosis of fibrillary glomerulonephritis

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Dock Yellow (Rumex crispus) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal 1 0.35 - 0.69 Low Positive 2 0.70 - 3.4 Moderate Positive 3 3.5 - 17.4 High Positive 4 17.5 - 49.9 Very High Positive 5 50.0 - 99.9 Very High Positive 6 > or = 100 Very High Positive

Reference Values: <0.35 kU/L

Dog Dander, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing may also be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of
allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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### DOG1 Immunostain, Technical Component Only

**Clinical Information:** DOG-1 (discovered on gastrointestinal stromal tumors GIST-1) is a calcium-regulated chloride channel protein that is expressed strongly on the cell surface of GISTs and rarely in other soft tissue tumors, such as uterine type retroperitoneal leiomyomas, peritoneal leiomyomatosis, and synovial sarcomas. DOG-1 may aid in the differential diagnosis of GISTs, including KIT-negative and PDGFRA-mutated GIST cases.

**Useful For:** Aids in the identification of gastrointestinal stromal tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
**Donath Landsteiner**

**Reference Values:**
Negative

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**FDLS**

**58007**

**DRD3O**

**60342**

**Dopamine Receptor D3 Genotype, Saliva**

**Clinical Information:** The neurotransmitter dopamine acts via dopamine receptors in the central nervous system. The atypical antipsychotic medications have high binding affinity for the polymorphic DRD3 receptor. The c.25G>A (rs6280) single nucleotide change within the DRD3 gene results in a change in the ninth encoded amino acid from glycine to serine (p.Gly9Ser); however, this variant is often referred to in the literature as the Ser9Gly polymorphism. This variant has been studied for associations with response to treatment with atypical antipsychotic medications of patients with schizophrenia, predisposition to schizophrenia, and risk for tardive dyskinesia. In addition, several more recent studies have evaluated the relationship between this variant and response to risperidone among patients with autism. While early studies suggested that this variant may be associated with response to clozapine among patients with treatment-resistant schizophrenia, a recent systematic review found that among 9 studies involving this variant only the initial 2 studies reported that the Gly variant was associated with a favorable response to clozapine, while all 7 subsequent studies (including the 2 with the largest sample size) found nonsignificant results.(1) Another recent systematic review and meta-analysis focused on risperidone treatment in patients with schizophrenia. Among 12 studies, this group found that although the Ser9Gly DRD3 variant was not associated with improvement in the positive and negative symptom scale (PANSS) score, it may be related to a change in negative symptoms.(2) Finally, another updated meta-analysis involving 73 studies for a total of 10,634 patients with schizophrenia and 11,258 controls found no association between the DRD3 Ser9Gly polymorphism and risk of schizophrenia.(3) A study involving 56 children with autism found that carriers of the Gly allele showed significantly better response to risperidone as compared with carriers of the Ser allele; however, this was a single study that has not yet been replicated.(4) In a study of 217 patients with Parkinson disease who were taking levodopa therapy, both the DRD3 rs6280 Ser/Ser genotype and the DRD2 rs1799732 Ins/Ins genotype were found to be independent predictors of levodopa-induced gastrointestinal symptoms.(5) Although this finding is of interest, it has not been replicated in a second cohort to date. The DRD3 c.25A>G, p.Gly9Ser polymorphism has been the most studied polymorphism in tardive dyskinesia (TD). Although early reports identified significant associations with the G allele and risk for TD and the initial meta-analysis also supported these findings,(6) the significance has decreased in more recent literature and meta-analyses.(7) Other variants in this gene have not been well studied.

**Useful For:** Predicting the likelihood of change in negative symptoms among patients with schizophrenia during risperidone therapy Predicting the response of children with autism to risperidone therapy Predicting the likelihood of gastrointestinal symptoms among patients with Parkinson disease treated with levodopa Genotyping patients who prefer not to have venipuncture done

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Dopamine Receptor D3 Genotype, Whole Blood

Clinical Information: The neurotransmitter dopamine acts via dopamine receptors in the central nervous system. The atypical antipsychotic medications have high binding affinity for the polymorphic DRD3 receptor. The c.25G>A (rs6280) single nucleotide change within the DRD3 gene results in a change in the ninth encoded amino acid from glycine to serine (p.Gly9Ser); however, this variant is often referred to in the literature as the Ser9Gly polymorphism. This variant has been studied for associations with response to treatment with atypical antipsychotic medications of patients with schizophrenia, predisposition to schizophrenia, and risk for tardive dyskinesia. In addition, several more recent studies have evaluated the relationship between this variant and response to risperidone among patients with autism. While early studies suggested that this variant may be associated with response to clozapine among patients with treatment resistant schizophrenia, a recent systematic review found that among 9 studies involving this variant only the initial 2 studies reported that the Gly variant was associated with a favorable response to clozapine, while all 7 subsequent studies (including the 2 with the largest sample size) found nonsignificant results. Another recent systematic review and meta-analysis focused on risperidone treatment in patients with schizophrenia. Among 12 studies, this group found that although the Ser9Gly DRD3 variant was not associated with improvement in the positive and negative symptom scale (PANSS) score, it may be related to a change in negative symptoms. Finally, another updated meta-analysis involving 73 studies for a total of 10,634 patients with schizophrenia and 11,258 controls found no association between the DRD3 Ser9Gly polymorphism and risk of schizophrenia. A study involving 56 children with autism found that carriers of the Gly allele showed significantly better response to risperidone as compared with carriers of the Ser allele; however, this was a single study that has not yet been replicated. In a study of 217 patients with Parkinson disease who were taking levodopa therapy, both the DRD3 rs6280 Ser/Ser genotype and the DRD2 rs1799732 Ins/Ins genotype were found to be independent predictors of levodopa-induced gastrointestinal symptoms. Although this finding is of interest, it has not been replicated in a second cohort to date. The DRD3 c.25A>G, p.Gly9Ser polymorphism has been the most studied polymorphism in tardive dyskinesia (TD). Although early reports identified significant associations with the G allele and risk for TD and the initial meta-analysis also supported these findings, the significance has decreased in more recent literature and meta-analyses. Other variants in this gene have not been well studied.

Useful For: Predicting the likelihood of change in negative symptoms among patients with schizophrenia during risperidone therapy Predicting the response of children with autism to risperidone therapy Predicting the likelihood of gastrointestinal symptoms among patients with Parkinson disease treated with levodopa

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.


**Dopamine Receptor D4 Genotype (DRD4), Blood**

**Clinical Information:** The dopamine receptor D4 gene (DRD4) is located near the telomeric region of chromosome 11q and is a highly variable gene. A 48-base pair (bp) variable number tandem repeat polymorphism in exon 3 of DRD4, which ranges from 2 to 11 repeats, creates a 32- to 176-amino acid variation in the third intracellular loop on the dopamine receptor. The frequency of these alleles is shown in the table. The DRD4 7-repeat allele (7R) has functional consequences and is associated with lower affinity for dopamine receptor agonists and reduced signal transduction (eg, cAMP levels) compared to the more common DRD4 4-repeat allele (4R). The effect of other copy number repeats is not as well defined to date. Frequency of alleles with various DRD4 exon 3 48-bp repeats: Allele/Number of repeats (R) Allelic Frequency (%) 2R 8.8 3R 2.4 4R 65.1 5R 1.6 6R 2.2 7R 19.2 8R 0.6 9R <0.1 10R <0.1 11R <0.1 The DRD4 protein is expressed in a number of brain regions, with higher levels of expression in the prefrontal cortex, where animal models suggest that it inhibits neuronal firing. Attention Deficit/Hyperactivity Disorder (ADHD): Several studies have found associations between the DRD4 7R allele and ADHD.(1,2) Similarly, a long form (240-bp variant) of a DRD4 promotor repeat polymorphism is associated with ADHD susceptibility, possibly due to linkage disequilibrium with the DRD4 7R allele.(3) Pharmacogenetics: Several studies demonstrate that the presence of the DRD4 7R allele, alone or in combination with the SLC6A4 long/long promotor polymorphism of the serotonin transporter, is associated with lower responsiveness of ADHD to methylphenidate (eg, Ritalin, Concerta), the main treatment for ADHD.(4) Methylphenidate dosage may have to be increased to effectively treat individuals with the DRD4 7R allele. The effect of other repeat numbers has not been defined to date and, if other alleles than the 4R and 7R are present, caution should be exercised in using methylphenidate to treat ADHD because the impact of these alleles on treatment response is not known. A recent meta-analysis found that children with a 4R/4R genotype had a 66% greater chance of responding to methylphenidate than those with other genotypes. Nonsignificant results were obtained when comparing the 7R variant to other genotypes.(5) Attempts to find an association between DRD4 genotype and the variability of response to antipsychotic drugs, especially clozapine, have been largely unsuccessful or have yielded conflicting results.

**Useful For:** Influencing the target dose of methylphenidate treatment for patients with attention deficit/hyperactivity disorder. Determining possible cause for poor response to methylphenidate in treated patients with attention deficit/hyperactivity disorder.

**Interpretation:** An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided.


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**Dopamine Receptor D4 Genotype (DRD4), Saliva**

**Clinical Information:** The dopamine receptor D4 gene (DRD4) is located near the telomeric region of chromosome 11q and is a highly variable gene. A 48-base pair (bp) variable number tandem repeat polymorphism in exon 3 of DRD4, which ranges from 2 to 11 repeats, creates a 32- to 176-amino acid variation in the third intracellular loop on the dopamine receptor. The frequency of these alleles is shown in the table. The DRD4 7-repeat allele (7R) has functional consequences and is associated with lower affinity for dopamine receptor agonists and reduced signal transduction (eg, cAMP levels) compared to the more common DRD4 4-repeat allele (4R). The effect of other copy number repeats is not as well defined to date. Frequency of alleles with various DRD4 exon 3 48-bp repeats: Allele/Number of repeats (R) Allelic Frequency (%) 2R 8.8 3R 2.4 4R 65.1 5R 1.6 6R 2.2 7R 19.2 8R 0.6 9R <0.1 10R <0.1 11R <0.1 The DRD4 protein is expressed in a number of brain regions, with higher levels of expression in the prefrontal cortex, where animal models suggest that it inhibits neuronal firing. Attention Deficit/Hyperactivity Disorder (ADHD): Several studies have found associations between the DRD4 7R allele and ADHD.(1,2) Similarly, a long form (240-bp variant) of a DRD4 promotor repeat polymorphism is associated with ADHD susceptibility, possibly due to linkage disequilibrium with the DRD4 7R allele.(3) Pharmacogenetics: Several studies demonstrate that the presence of the DRD4 7R allele, alone or in combination with the SLC6A4 long/long promotor polymorphism of the serotonin transporter, is associated with lower responsiveness of ADHD to methylphenidate (eg, Ritalin, Concerta), the main treatment for ADHD.(4) Methylphenidate dosage may have to be increased to effectively treat individuals with the DRD4 7R allele. The effect of other repeat numbers has not been defined to date and, if other alleles than the 4R and 7R are present, caution should be exercised in using methylphenidate to treat ADHD because the impact of these alleles on treatment response is not known. A recent meta-analysis found that children with a 4R/4R genotype had a 66% greater chance of responding to methylphenidate than those with other genotypes. Nonsignificant results were obtained when comparing the 7R variant to other genotypes.(5) Attempts to find an association between DRD4 genotype and the variability of response to antipsychotic drugs, especially clozapine, have been largely unsuccessful or have yielded conflicting results.

**Useful For:** Influencing the target dose of methylphenidate treatment for patients with attention deficit/hyperactivity disorder. Determining possible cause for poor response to methylphenidate in treated patients with attention deficit/hyperactivity disorder.

**Interpretation:** An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided.

Clinical Information: The dopamine receptor D4 gene (DRD4) is located near the telomeric region of chromosome 11q and is a highly variable gene. A 48-base pair (bp) variable number tandem repeat (VNTR) polymorphism in exon 3 of DRD4, which ranges from 2 to 11 repeats, creates a 32- to 176-amino acid variation in the third intracellular loop on the dopamine receptor. The frequency of these alleles is shown in Table 1. The DRD4 7-repeat allele (7R) has functional consequences and is associated with lower affinity for dopamine receptor agonists and reduced signal transduction (eg, cAMP levels) compared to the more common DRD4 4-repeat allele (4R). The effect of other copy number repeats is not as well defined to date, however, and VNTRs with 6 or fewer repeats are grouped as 4R and those with 7 or more repeats as 7R. Frequency of alleles with various DRD4 exon 3 48-bp repeats: Allele/Number of Repeats (R) Allelic Frequency (%) 2R 8.8 3R 2.4 4R 65.1 5R 0.6 6R 0.6 7R 19.2 8R <0.1 9R <0.1 The DRD4 protein is expressed in a number of brain regions, with higher levels of expression in the prefrontal cortex, where animal models suggest that it inhibits neuronal firing. Attention Deficit/Hyperactivity Disorder (ADHD): Several studies have found associations between the DRD4 7R allele and ADHD. Similarly, a long form (240-bp variant) of a DRD4 promotor repeat polymorphism is associated with ADHD susceptibility, possibly due to linkage disequilibrium with the DRD4 7R allele. Pharmacogenetics: Several studies demonstrate that the presence of the DRD4 7R allele, alone or in combination with the SLC6A4 long/long promotor polymorphism of the serotonin transporter, is associated with lower responsiveness of ADHD to methylphenidate (eg, Ritalin, Concerta), the main treatment for ADHD. Methylphenidate dosage may have to be increased to effectively treat individuals with the DRD4 7R allele. Attempts to find an association between DRD4 genotype and the variability of response to antipsychotic drugs, especially clozapine, have been largely unsuccessful or have yielded conflicting results. A recent meta-analysis found that children with a 4R/4R genotype had a 66% greater chance of responding to methylphenidate than those with other genotypes. Nonsignificant results were obtained when comparing the 7R variant to other genotypes.

Useful For: Influencing the target dose of methylphenidate treatment for patients with attention deficit/hyperactivity disorder Determining possible cause for poor response to methylphenidate in treated patients with attention deficit/hyperactivity disorder Genotyping patients who prefer not to have venipuncture done

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.


Douglas Fir, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>Interpretation</th>
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</thead>
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</tr>
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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Doxepin and Nordoxepin, Serum**

**Clinical Information:** Doxepin is recommended for the treatment of psychoneurotic patients with depression or anxiety, and depression or anxiety associated with alcoholism or organic disease. Nordoxepin (N-desmethyldoxepin) is the major metabolite and is usually present at concentrations equal to doxepin. Optimal efficacy occurs at combined serum concentrations between 50 and 150 ng/mL. Like other tricyclic antidepressants, the major toxicity of doxepin is expressed as cardiac dysrhythmias, which occur at concentrations in excess of 500 ng/mL. Other side effects include nausea, hypotension, and dry mouth.

**Useful For:** Monitoring therapy Evaluating potential toxicity Evaluating patient compliance

**Interpretation:** Most individuals display optimal response to doxepin when combined serum levels of doxepin and nordoxepin are between 50 and 150 ng/mL. Some individuals may respond well outside of this range, or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Risk of toxicity is increased with combined levels are above 500 ng/mL. Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next dose).

**Reference Values:**

Therapeutic concentration (doxepin + nordoxepin): 50-150 ng/mL

Note: Therapeutic ranges are for specimens drawn at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.

**Clinical References:** 1. Wille SM, Cooreman SG, Neels HM, Lambert WE: Relevant issues in the
Drug Abuse Panel with Confirmation, Chain of Custody, Urine

Clinical Information: This assay was designed to screen for and confirm by gas chromatography-mass spectrometry (GC-MS), gas chromatography-flame ionization detection (GC-FID), or liquid chromatography-tandem mass spectrometry (LC-MS/MS) for the following drugs: -Amphetamines -Barbiturates -Benzodiazepines -Cocaine -Ethanol -Opiates -Phencyclidine -Tetrahydrocannabinol Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detecting drug abuse involving amphetamines, barbiturates, benzodiazepines, cocaine, ethanol, marijuana, opiates, and phencyclidine This test is intended to be used in a setting where the test results can be used definitively to make a diagnosis. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (eg, AMPHX / Amphetamines Confirmation, Chain of Custody, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at http://www.mayomedicallaboratories.com/test-info/drug-book/index.html

Reference Values:
Negative
Screening cutoff concentrations
Amphetamines: 500 ng/mL
Barbiturates: 200 ng/mL
Benzodiazepines: 100 ng/mL
Cocaine (benzoylcegonine-cocaine metabolite): 150 ng/mL
Ethanol: 10 mg/dL
Opiates: 300 ng/mL
Phencyclidine: 25 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL
This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.


Drug Abuse Survey with Confirmation, Panel 5, Chain of Custody, Urine

Clinical Information: This assay was designed to screen for and confirm by gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-tandem mass spectrometry (LC-MS/MS) the following drugs: -Amphetamines -Cocaine -Opiates -Phencyclidine

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Tetrahydrocannabinol Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Useful For:** Detecting drug abuse involving amphetamines, cocaine, marijuana, opiates, and phencyclidine This chain-of-custody test is intended to be used in a setting where the test results can be used definitively to make a diagnosis.

**Reference Values:**

- **Negative**
- Screening cutoff concentrations
  - Amphetamines: 500 ng/mL
  - Cocaine (benzoylecegonine-cocaine metabolite): 150 ng/mL
  - Opiates: 300 ng/mL
  - Phencyclidine: 25 ng/mL
  - Tetrahydrocannabinol carboxylic acid: 50 ng/mL

This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.

**Clinical References:**


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**CDAU5 80373**

**Drug Abuse Survey with Confirmation, Panel 5, Urine**

**Clinical Information:** This assay was designed to screen for and confirm by gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-tandem mass spectrometry (LC-MS/MS) for the following drugs: -Amphetamines -Cocaine -Opiates -Phencyclidine -Tetrahydrocannabinol This assay represents the coupling of UDOA / Drug Abuse Survey, Urine with an automatic confirmation of all positive results by the definitive assay available and described elsewhere (eg, AMPHU / Amphetamines Confirmation, Urine). All positive screening results are confirmed by GC-MS or LC-MS/MS, and quantitated, before a positive result is reported.

**Useful For:** Detecting drug abuse involving amphetamines, cocaine, marijuana, opiates, and phencyclidine This test is intended to be used in a setting where the test results can be used definitively to make a diagnosis. Some drug treatment programs do not require confirmatory testing of screen-positive specimens. In those settings, UDOA / Drug Abuse Survey, Urine is a less costly option.

**Interpretation:** A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (eg, AMPHU / Amphetamines Confirmation, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at http://www.mayomedicallaboratories.com/test-info/drug-book/index.html

**Reference Values:**

- **Negative**
- Screening cutoff concentrations
  - Amphetamines: 500 ng/mL
  - Cocaine (benzoylecegonine-cocaine metabolite): 150 ng/mL
  - Opiates: 300 ng/mL
  - Phencyclidine: 25 ng/mL
  - Tetrahydrocannabinol carboxylic acid: 50 ng/mL

This report is intended for use in clinical monitoring or management of patients. It is not intended for use...
in employment-related testing.


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**Drug Abuse Survey with Confirmation, Panel 9, Chain of Custody, Urine**

**Clinical Information:** This assay was designed to test for and confirm by gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-tandem mass spectrometry (LC-MS/MS) the most common classes of drugs of abuse. This test uses the simple screening technique which involves immunologic testing for drugs by class. All positive screening results are confirmed by GC-MS (positive alcohol by GC) or LC-MS/MS and quantitated, before a positive result is reported. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Useful For:** Detecting drug abuse involving alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, and tetrahydrocannabinol. This chain-of-custody test is intended to be used in a setting where the test results can be used definitively to make a diagnosis.

**Interpretation:** A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (eg, AMPHX / Amphetamines Confirmation, Chain of Custody, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at http://www.mayomedicallaboratories.com/test-info/drug-book/index.html

**Reference Values:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>500 ng/mL</td>
</tr>
<tr>
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<td>200 ng/mL</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>100 ng/mL</td>
</tr>
<tr>
<td>Cocaine</td>
<td>150 ng/mL</td>
</tr>
<tr>
<td>Ethanol</td>
<td>10 mg/dL</td>
</tr>
<tr>
<td>Methadone metabolite</td>
<td>300 ng/mL</td>
</tr>
<tr>
<td>Opiates</td>
<td>300 ng/mL</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>25 ng/mL</td>
</tr>
<tr>
<td>Tetrahydrocannabinol</td>
<td>50 ng/mL</td>
</tr>
</tbody>
</table>

This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.


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**Drug Abuse Survey with Confirmation, Panel 9, Urine**

**Clinical Information:** This assay was designed to test for and confirm by gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-tandem mass spectrometry (LC-MS/MS) the most common classes of drugs of abuse. This test uses the simple screening technique which involves immunologic testing for drugs by class. All positive screening results are confirmed by GC-MS (positive alcohol by GC) or LC-MS/MS and quantitated, before a positive result is reported. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Useful For:** Detecting drug abuse involving alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, and tetrahydrocannabinol. This chain-of-custody test is intended to be used in a setting where the test results can be used definitively to make a diagnosis.

**Interpretation:** A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (eg, AMPHX / Amphetamines Confirmation, Chain of Custody, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at http://www.mayomedicallaboratories.com/test-info/drug-book/index.html

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chromatography-mass spectrometry (GC-MS) or liquid chromatography-tandem mass spectrometry (LC-MS/MS) the most common classes of drugs of abuse. This test uses the simple screening technique which involves immunologic testing for drugs by class. All positive screening results are confirmed by GC-MS (positive alcohol by GC) or LC-MS/MS, and quantitated, before a positive result is reported. This test represents the coupling of UDOA / Drug Abuse Survey, Urine with an automatic confirmation of all positive results by the definitive assay available and described elsewhere (eg, AMPHU / Amphetamines Confirmation, Urine).

**Useful For:** Detecting drug abuse involving alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, and tetrahydrocannabinol This test is intended to be used in a setting where the test results can be used definitively to make a diagnosis

**Reference Values:**

**Negative**

Screening cutoff concentrations
- Amphetamines: 500 ng/mL
- Barbiturates: 200 ng/mL
- Benzodiazepines: 100 ng/mL
- Cocaine (benzoylecgonine-cocaine metabolite): 150 ng/mL
- Ethanol: 10 mg/dL
- Methadone metabolite: 300 ng/mL
- Opiates: 300 ng/mL
- Phencyclidine: 25 mg/mL
- Tetrahydrocannabinol carboxylic acid: 50 ng/mL

This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.

**Clinical References:**
Drug Screen, Prescription/OTC, Chain of Custody, Serum

Clinical Information: This test looks for a broad spectrum of prescription and over-the-counter (OTC) drugs. It is designed to detect drugs that have toxic effects, as well as known antidotes or active therapies that a clinician can initiate to treat the toxic effect. The test is intended to help physicians manage an apparent overdose or intoxicated patient, to determine if a specific set of symptoms might be due to the presence of drugs, or to evaluate a patient who might be abusing these drugs intermittently. This test is not appropriate for drugs of abuse or illicit drug testing, including benzodiazepines, opioids, barbiturates, cocaine, amphetamine type stimulants. Drugs of toxic significance that are not detected by this test are: digoxin, lithium, and many drugs of abuse or illicit drugs, some benzodiazepines, and most opiates. See Prescription and Over-the-Counter (OTC) Drug Screens Table 1 in Special Instructions for detection limits for drugs detected in this test. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Detection and identification of prescription or over the counter drugs frequently found in drug overdose or used with a suicidal intent This test is designed to qualitatively identify drugs present in the specimen; quantification of identified drugs, when available, may be performed upon client request. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: The drugs that are detected by this test are listed in Prescription and Over-the-Counter (OTC) Drug Screens Table 1 in Special Instructions. The pharmacology of each drug determines how the test should be interpreted. A detailed discussion of each drug is beyond the scope of this text. If you wish to have a report interpreted, call 800-533-1710 and ask for a toxicology consultant. Each report will indicate the drugs detected.

Reference Values: Drugs detected are presumptive. Additional testing may be required to confirm the presence of any drugs detected.

Drug Screen, Prescription/OTC, Chain of Custody, Urine

Clinical Information: This test looks for a broad spectrum of prescription and over-the-counter (OTC) drugs. It is designed to detect drugs that have toxic effects, as well as known antidotes or active therapies that a clinician can initiate to treat the toxic effect. The test is intended to help physicians manage an apparent overdose or intoxicated patient, to determine if a specific set of symptoms might be due to the presence of drugs, or to evaluate a patient who might be abusing these drugs intermittently. This test is not appropriate for drugs of abuse or illicit drug testing, including benzodiazepines, opioids, barbiturates, cocaine, amphetamine type stimulants. Drugs of toxic significance that are not detected by this test are: digoxin, lithium, and many drugs of abuse or illicit drugs, some benzodiazepines, and some opiates. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. See Prescription and Over-the-Counter (OTC) Drug Screens in Special Instructions for detection limits for drugs detected in this test.

Useful For: The qualitative detection and identification of prescription or over-the-counter drugs frequently found in drug overdose or used with a suicidal intent. This test is designed to provide, when possible, the identification of all drugs present. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: The drugs that can be detected by this test are listed in Prescription and Over-the-Counter (OTC) Drug Screens in Special Instructions. Drugs of toxic significance that are not detected by this test include digoxin, lithium, many drugs of abuse or illicit drugs, some benzodiazepines, and some opiates. For these drugs, see Mayo Medical Laboratories' drug abuse surveys or drug screens or individual tests. A detailed discussion of each drug detected is beyond the scope of this text. Each report will indicate the drugs identified. If a clinical interpretation is required, request a Drug/Toxicology Lab consult (Mayo Clinic patients) or contact Mayo Laboratory Inquiry (Mayo Medical Laboratories clients).

Reference Values:
Drugs detected are presumptive. Additional testing may be required to confirm the presence of any drugs detected.


Drug Screen, Prescription/OTC, Serum

Clinical Information: This test looks for a broad spectrum of prescription and over-the-counter (OTC) drugs. It is designed to detect drugs that have toxic effects, as well as known antidotes or active therapies that a clinician can initiate to treat the toxic effect. The test is intended to help physicians manage an apparent overdose or intoxicated patient, or to determine if a specific set of symptoms might be due to the presence of drugs. This test is not appropriate for drugs of abuse or illicit drug testing, including benzodiazepines, opioids, barbiturates, cocaine, amphetamine type stimulants. Drugs of toxic significance that are not detected by this test are: digoxin, lithium, and many drugs of abuse or illicit drugs, some benzodiazepines, and some opiates. See Prescription and Over-the-Counter (OTC) Drug Screens in Special Instructions for detection limits for drugs detected in this test.

Useful For: Detection and identification of prescription or over the counter drugs frequently found in drug overdose or used with a suicidal intent. This test is designed to qualitatively identify drugs present in the specimen; quantification of identified drugs, when available, may be performed upon client request.

Interpretation: The drugs that are detected by this test are listed in Prescription and Over-the-Counter
(OTC) Drug Screens in Special Instructions. The pharmacology of each drug determines how the test should be interpreted. A detailed discussion of each drug is beyond the scope of this text. If you wish to have a report interpreted, call 800-533-1710 and ask for a toxicology consultant. Each report will indicate the drugs detected.

**Reference Values:**
Drugs detected are presumptive. Additional testing may be required to confirm the presence of any drugs detected.

**Clinical References:**

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**Drug Screen, Prescription/OTC, Urine**

**Clinical Information:** This test looks for a broad spectrum of prescription and over-the-counter (OTC) drugs. It is designed to detect drugs that have toxic effects, as well as known antidotes or active therapies that a clinician can initiate to treat the toxic effect. The test is intended to help physicians manage an apparent overdose or intoxicated patient, or to determine if a specific set of symptoms might be due to the presence of drugs. This test is not appropriate for drugs of abuse or illicit drug testing, including benzodiazepines, opioids, barbiturates, cocaine, amphetamine type stimulants. Drugs of toxic significance that are not detected by this test are: digoxin, lithium, and many drugs of abuse or illicit drugs, some benzodiazepines, and some opioids. See Prescription and Over-the-Counter (OTC) Drug Screens in Special Instructions for detection limits for drugs detected in this test.

**Useful For:** The qualitative detection and identification of prescription or over-the-counter drugs frequently found in drug overdose or used with a suicidal intent. This test is designed to provide, when possible, the identification of all drugs present.

**Interpretation:** The drugs that can be detected by this test are listed in Prescription and Over-the-Counter (OTC) Drug Screens in Special Instructions. Drugs of toxic significance that are not detected by this test include digoxin, lithium, many drugs of abuse/illicit drugs, some benzodiazepines, and some opiates. For these drugs, see Mayo Medical Laboratories' drug abuse surveys or drug screens or individual tests. A detailed discussion of each drug detected is beyond the scope of this text. Each report will indicate the drugs identified. If a clinical interpretation is required, request a Drug/Toxicology Lab consult (Mayo Clinic patients) or contact Mayo Laboratory Inquiry (Mayo Medical Laboratories clients).

**Reference Values:**
Drugs detected are presumptive. Additional testing may be required to confirm the presence of any drugs detected.

**Clinical References:**

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**Drugs of Abuse Screen 4, Chain of Custody, Meconium**

**Clinical Information:** Illicit drug use during pregnancy is a major social and medical issue. Drug abuse during pregnancy is associated with significant perinatal complications, which include a high incidence of stillbirths, meconium-stained fluid, premature rupture of the membranes, maternal hemorrhage (abruption placenta or placenta praevia), and fetal distress.(1) In the neonate, the mortality rate, as well as morbidity (e.g., asphyxia, prematurity, low birthweight, hyaline membrane distress,
infections, aspiration pneumonia, cerebral infarction, abnormal heart rate and breathing problems, drug withdrawal) are increased. (1) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid. (2) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation. (3) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure up to 5 months before birth, a longer historical measure than is possible by urinalysis. (2) Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Identifying amphetamines (and methamphetamines), opiates, as well as metabolites of cocaine and marijuana in meconium specimen Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

Interpretation: The limit of quantitation varies for each of these drug groups. - Amphetamines: >100 ng/g - Methamphetamines: >100 ng/g - Cocaine and metabolite: >100 ng/g - Opiates: >100 ng/g - Tetrahydrocannabinol carboxylic acid: >20 ng/g

Reference Values:
Negative
Positives are reported with a quantitative LC-MS/MS result.
Cutoff concentrations
Amphetamines by ELISA: 100 ng/g
Methamphetamine by ELISA: 100 ng/g
Benzoylcegonine (cocaine metabolite) by ELISA: 100 ng/g
Opiates by ELISA: 100 ng/g
Tetrahydrocannabinol carboxylic acid (marijuana metabolite) by ELISA: 20 ng/g


Drugs of Abuse Screen 5, Chain of Custody, Meconium

Clinical Information: Illicit drug use during pregnancy is a major social and medical issue. Drug abuse during pregnancy is associated with significant perinatal complications, which include a high incidence of stillbirths, meconium-stained fluid, premature rupture of the membranes, maternal hemorrhage (abruption placenta or placenta praevia), and fetal distress. (1) In the neonate, the mortality rate, as well as morbidity (e.g., asphyxia, prematurity, low birthweight, hyaline membrane disease, infections, aspirations pneumonia, cerebral infarction, abnormal heart rate and breathing patterns, drug withdrawal) are increased. (1) The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid. (2) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation. (3) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis. (2) Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand...
regular court scrutiny.

**Useful For:** Identifying amphetamines (and methamphetamines), opiates, as well as metabolites of cocaine and marijuana in meconium specimens. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

**Interpretation:** The limit of quantitation varies for each of these drug groups. -Amphetamines: >100 ng/g -Methamphetamines: >100 ng/g -Cocaine and metabolite: >100 ng/g -Opiates: >100 ng/g -Tetrahydrocannabinol carboxylic acid: >20 ng/g -Phencyclidine (PCP): >20 ng/g

**Reference Values:**

- **Negative**
- Positives are reported with a quantitative LC-MS/MS result.
- Cutoff concentrations
  - Amphetamines by ELISA: 100 ng/g
  - Methamphetamine by ELISA: 100 ng/g
  - Benzoylecgonine (cocaine metabolite) by ELISA: 100 ng/g
  - Opiates by ELISA: 100 ng/g
  - Tetrahydrocannabinol carboxylic acid (marijuana metabolite) by ELISA: 20 ng/g
  - Phencyclidine by ELISA: 20 ng/g

**Clinical References:**


**Drugs of Abuse Screen, Meconium 4**

**Clinical Information:** Illicit drug use during pregnancy is a major social and medical issue. Drug abuse during pregnancy is associated with significant perinatal complications, which include a high incidence of stillbirths, meconium-stained fluid, premature rupture of the membranes, maternal hemorrhage (abruption placenta or placenta previa), and fetal distress. In the neonate, the mortality rate, as well as morbidity (eg, asphyxia, prematurity, low birthweight, hyaline membrane distress, infections, aspiration pneumonia, cerebral infarction, abnormal heart rate and breathing problems, drug withdrawal) are increased. The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid. The first evidence of meconium in the fetal intestine appears at approximately the tenth to twelfth week of gestation, and slowly moves into the colon by the sixteenth week of gestation. Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.

**Useful For:** Identifying amphetamines (and methamphetamines), opiates, as well as metabolites of cocaine and marijuana in meconium specimens.

**Interpretation:** A positive result indicates that the baby was exposed to the drugs indicated.

**Reference Values:**

- **Negative**
  - Positives are reported with a quantitative LC-MS/MS result.
  - Cutoff concentrations
    - Amphetamines by ELISA: 100 ng/g
    - Methamphetamine by ELISA: 100 ng/g
Benzoylcegonine (cocaine metabolite) by ELISA: 100 ng/g
Opiates by ELISA: 100 ng/g
Tetrahydrocannabinol carboxylic acid (marijuana metabolite) by ELISA: 20 ng/g


Drugs of Abuse Screen, Meconium 5

Clinical Information: Illicit drug use during pregnancy is a major social and medical issue. Drug abuse during pregnancy is associated with significant perinatal complications, which include a high incidence of stillbirths, meconium-stained fluid, premature rupture of the membranes, maternal hemorrhage (abruption placenta or placenta praevia), and fetal distress. In the neonate, the mortality rate, as well as morbidity (e.g., asphyxia, prematurity, low birthweight, hyaline membrane disease, infections, aspirations pneumonia, cerebral infarction, abnormal heart rate and breathing patterns, drug withdrawal) are increased. The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid. The first evidence of meconium in the fetal intestine appears at approximately the tenth to twelfth week of gestation, and slowly moves into the colon by the sixteenth week of gestation. Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.

Useful For: Identifying amphetamines (and methamphetamines), opiates, phencyclidine (PCP), as well as metabolites of cocaine and marijuana in meconium specimens

Interpretation: A positive result indicates that the baby was exposed to the drugs indicated.

Reference Values:
Negative
Positives are reported with a quantitative LC-MS/MS result.
Cutoff concentrations
Amphetamines by ELISA: 100 ng/g
Methamphetamine by ELISA: 100 ng/g
Benzoylcegonine (cocaine metabolite) by ELISA: 100 ng/g
Opiates by ELISA: 100 ng/g
Tetrahydrocannabinol carboxylic acid (marijuana metabolite) by ELISA: 20 ng/g
Phencyclidine by ELISA: 20 ng/g

muscle affected in DMD, but also the smooth muscle of the gastrointestinal tract and possibly bladder, as well as cardiac muscle. Initial symptoms are followed by dramatic progression of weakness leading to loss of ambulation by age 11 or 12. Death is often caused by cardiac failure or by respiratory failure before age 30, unless ventilator support is provided. The allelic Becker muscular dystrophy (BMD) has a similar presentation, although age of onset is later and the clinical course is much milder. Cardiac involvement can be the only sign and patients are often ambulatory into their thirties. DMD and BMD are caused by mutations in the DMD gene, which encodes for dystrophin. Approximately 50% to 65% of patients have intragenic deletions and approximately 5% to 10% have intragenic duplications. Less frequently, DMD and BMD result from nondeletion and nonduplication mutations, which are not detected by this assay. Approximately one-third of sporadic cases of DMD/BMD occur due to new mutations. In sporadic cases, it is possible for the mother of an affected individual to have germline mosaicism. This means that the germ cells may contain a mutation even if the mutation is not detected in peripheral blood. In cases of germline mosaicism, which occurs with a frequency of up to 15%, further offspring are at risk for inheriting a dystrophin mutation.

Useful For:
- Confirmation of a clinical diagnosis of Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD)
- Distinguishing DMD from BMD in some cases, based on the type of deletion detected (allows for better prediction of prognosis)
- Determination of carrier status in family member at risk for DMD or BMD
- Prenatal diagnosis of DMD or BMD in at-risk pregnancies

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References:

Duck Feathers, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L  Interpretation

0  Negative

1  0.35-0.69  Equivocal

2  0.70-3.49  Positive

3  3.50-17.4  Positive

4  17.5-49.9  Strongly positive

5  50.0-99.9  Strongly positive

6  > or =100  Strongly positive

Reference values apply to all ages.


Duck Meat IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values: <0.35 kU/L

Duloxetine, Serum

Clinical Information: Duloxetine is an antidepressant of the serotonin-norepinephrine reuptake inhibitor class. It is effective in treating symptoms of depression, including physical pain associated with depression; other uses include therapy of neuropathic pain, fibromyalgia, and urinary stress incontinence. Duloxetine also inhibits serotonin uptake in human platelets, and may be associated with potentiation of bleeding. Duloxetine undergoes extensive hepatic biotransformation to numerous inactive metabolites. The drug is metabolized by CYP1A2 and CYP2D6, with moderate potential for drug interactions (duloxetine is both a substrate and a moderate inhibitor of CYP2D6). The mean elimination half-life is 12.5 hours with steady-state concentrations occurring in about 3 days. Specimens for therapeutic monitoring should be drawn immediately before the next scheduled dose (ie, trough). Duloxetine is not recommended for patients with hepatic impairment, substantial alcohol use, or chronic liver disease. Use in patients with renal disease significantly increases exposure to duloxetine due to decreased elimination. Patients with mild-to-moderate renal dysfunction should be monitored closely; use of duloxetine is not recommended in end-stage renal disease.

Useful For: Monitoring serum concentration during therapy Evaluating potential toxicity Evaluating patient compliance

Interpretation: Therapeutic ranges are not well-established, but literature suggests that patients receiving duloxetine monotherapy for depression responded well when trough concentrations were 60 to 120 ng/mL. Higher levels may be tolerated by individual patients. The therapeutic relevance of this concentration range to other uses of duloxetine therapy is currently unknown.

Reference Values: 60-120 ng/mL


**ECAD**

**E-Cadherin Immunostain, Bone Marrow, Technical Component Only**

**Clinical Information:** Membrane protein expressed on normal breast epithelial cells. Expression can be lost on lobular neoplasms of the breast, in contrast to ductal neoplasms of the breast.

**Useful For:** Aiding in differentiation between lobular and ductal neoplasms of the breast

**Interpretation:**
This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**ECAD**

**E-Cadherin Immunostain, Technical Component Only**

**Clinical Information:** Membrane protein expressed on normal breast epithelial cells. Expression can be lost on lobular neoplasms of the breast, in contrast to ductal neoplasms of the breast.

**Useful For:** Aids in differentiation between lobular and ductal neoplasms of the breast

**Interpretation:**
This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
Eastern Equine Encephalitis Antibody Panel, IgG and IgM, Spinal Fluid

**Clinical Information:** Eastern equine encephalitis (EEE) is within the alphavirus group. It is a low-prevalence cause of human disease in the Eastern and Gulf Coast states. EEE is maintained by a cycle of mosquito/wild bird transmission, peaking in the summer and early fall, when man may become an adventitious host. The most common clinically apparent manifestation is a mild undifferentiated febrile illness, usually with headache. Central nervous system involvement is demonstrated in only a minority of infected individuals, and is more abrupt and more severe than with other arboviruses, with children being more susceptible to severe disease. Fatality rates are approximately 70% for EEE. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod, relating to age, sex, and occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age.

**Useful For:** Aiding the diagnosis of Eastern equine encephalitis in spinal fluid specimens

**Interpretation:** Detection of organism-specific antibodies in the cerebrospinal fluid (CSF) may suggest central nervous system (CNS) infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of CNS infection.

**Reference Values:**
- IgG: <1:10
- IgM: <1:10

Reference values apply to all ages.

**Clinical References:**

Eastern Equine Encephalitis Antibody, IgG and IgM, Serum

**Clinical Information:** Eastern equine encephalitis (EEE) is within the alphavirus group. It is a low prevalence cause of human disease in the Eastern and Gulf Coast states. EEE is maintained by a cycle of mosquito/wild bird transmission, peaking in the summer and early fall, when man may become an adventitious host. The most common clinically apparent manifestation is a mild undifferentiated febrile illness, usually with headache. Central nervous system involvement is demonstrated in only a minority of infected individuals, it is more abrupt and more severe with EEE than other arboviruses, with children being more susceptible to severe disease. Fatality rates are approximately 70% for EEE.

**Useful For:** Aiding in the diagnosis of Eastern equine encephalitis

**Interpretation:** In patients infected with this virus, IgG antibody is generally detectable within 1 to 3 weeks of onset, peaking within 1 to 2 months, and declining slowly thereafter. IgM class antibody is also reliably detected within 1 to 3 weeks of onset, peaking and rapidly declining within 3 months. Single serum specimen IgG > or =1:10 indicates exposure to the virus. Results from a single serum specimen can differentiate early (acute) infection from past infection with immunity if IgM is positive (suggests acute...
infection). A 4-fold or greater rise in IgG antibody titer in acute and convalescent sera indicate recent infection. In the United States it is unusual for any patient to show positive reactions to more than 1 of the arboviral antigens, although Western equine encephalitis and Eastern equine encephalitis antigens will show a noticeable cross-reactivity. Infections can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age and sex, as well as the occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age.

Reference Values:
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

Clinical References:

Eastern Sycamore, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive

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**Echinococcus Antibody, IgG, Serum**

**Clinical Information:** Echinococcosis, also referred to as hydatidosis or hydatid disease, is one of the 17 neglected tropical diseases recognized by the World Health Organization, and affects over 1 million people worldwide. Echinococcus species are tapeworms or cestodes and 2 main species infect humans: E granulosus and E multilocularis. With respect to geographic distribution, E granulosus can be found worldwide, but more frequently in rural grazing areas where dogs may feed on infected sheep or cattle carcasses. E multilocularis is largely localized to the northern hemisphere. The definitive hosts for E granulosus are dogs or other canids, while the definitive host for E multilocularis are foxes and, to a much lesser extent, canids. Echinococcus tapeworms reside in the small intestine of definitive hosts and release eggs that are passed in the feces and ingested by an intermediate host, typically sheep or cattle in the case of E granulosus or small rodents for E multilocularis. The eggs hatch in the small bowel, releasing an oosphore, which penetrates the intestinal wall and migrates through the circulatory system to various organs where it will develop into a cyst that gradually enlarges producing protoscolieis and daughter cysts that fill the interior. The definitive host becomes infected following ingestion of these infectious cysts. Humans become accidentally infected following ingestion of Echinococcus eggs. In humans, E granulosus (cystic echinococcal disease) cysts typically develop in the lungs and liver and the infection may remain silent or latent for years (5-20 years) prior to cyst enlargement and symptom manifestation. Symptomatic manifestations include chest pain, hemoptysis, and cough for pulmonary involvement and abdominal pain and biliary duct obstruction for liver infection. E multilocularis (alveolar echinococcal disease) infections manifest more rapidly than those of E granulosus, and manifests similar to a rapidly growing, destructive tumor resulting in abdominal pain and biliary obstruction. Rupture of cysts can produce fever, urticaria, and anaphylactic shock. Diagnosis of echinococcal infections relies on characteristic finding by ultrasound or other imaging techniques and serologic findings. Fine-needle aspirates of cystic fluid may be performed; however, they carry the risk of cyst puncture and fluid leakage, which may potentially lead to severe allergic reactions. Importantly, infected individuals do not shed eggs in stool.

**Useful For:** Detection of antibodies to Echinococcus species, including E multilocularis and E granulosus

**Interpretation:**
- **Negative:** The absence of antibodies to Echinococcus species suggests that the individual has not been exposed to this cestode. A single negative result should not be used to rule out infection (see Cautions). Equivocal: consider repeat testing on a new serum sample in 1 to 2 weeks.
- **Positive:** Results suggest infection with Echinococcus. False-positive results may occur in settings of infection with other helminths, or in patients with chronic immune disorders. Results should be considered alongside other clinical findings (e.g., characteristic findings on imaging) and exposure history.

**Reference Values:**

- **Negative**
- **Reference values apply to all ages.

**Clinical References:**

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**Eculizumab Monitoring Panel, Serum**

**Clinical Information:** Eculizumab (Soliris, Alexion Pharmaceuticals) is a humanized hybrid...
monoclonal antibody (IgG2/IgG4) that blocks complement C5 cleavage, thereby preventing the activation of the proinflammatory effects of C5a and the cytolytic effects of the membrane attack complex (MAC) formed by C5b-C9. It is FDA-approved for atypical hemolytic uremic syndrome, (1) and paroxysmal nocturnal hemoglobinuria, (2) and also prescribed for other conditions such as C3 glomerulopathies. (3) The dosing regimen for an average adult may vary from 300 to 1200 mg intravenously every 2 weeks during the maintenance stages, according to the condition for which the drug is prescribed. Therapy efficacy may be monitored by measuring efficiency of complement blockade. (4) Eculizumab will affect complement function assays that rely on the formation of the MAC to generate cell lysis. Although CH50 and sMAC have been recommended for eculizumab monitoring, the measurement of C5 function and C5 antigen will more specifically indicate the impact of eculizumab on the complement system blockade and may help guide the next dose of the drug. This panel measures the pharmacodynamics effects of eculizumab on the complement system.

**Useful For:** Therapeutic drug monitoring of eculizumab

**Interpretation:** The panel will measure the pharmacodynamic effects of eculizumab on the complement system. Total complement function (CH50), alternative pathway function (AH50), and C5 function assays will be decreased to a similar extent in the presence of eculizumab. The function of C5 may be completely absent when eculizumab is present at therapeutic concentrations. C5 antigen, on the other hand, will be normal or elevated. C5 complement function drops on average 30% with 25 mcg/mL of eculizumab, and 70% with 50 mcg/mL. In the presence of 100 mcg/mL of eculizumab in serum, there is an average 20% residual C5 function. Decreased C5 function in the presence of normal or elevated C5 antigen concentrations suggests eculizumab is partially blocking C5 activity. Absent C5 function in the presence of normal or elevated C5 antigen concentrations suggests eculizumab is completely blocking C5 activity. Normal C5 function in the presence of normal or elevated C5 antigen concentrations suggests eculizumab concentration is not sufficient to block C5 activity. If C5 function and C5 antigen concentrations are all decreased, it may be due to a secondary consumption process, poor hepatic synthesis of complement proteins or C5 deficiency. Clinical correlation recommended. If indicated, resubmit samples to confirm results.

**Reference Values:**

- C5 COMPLEMENT ANTIGEN
  - 10.6-26.3 mg/dL

- C5 COMPLEMENT FUNCTIONAL
  - 29-53 U/mL

**Clinical References:**


**Eculizumab, Serum**

**Clinical Information:** Eculizumab (Soliris, Alexion Pharmaceuticals), a humanized monoclonal IgG2/4 kappa antibody therapeutic directed against complement component C5, has been heralded as a breakthrough treatment for paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS). By association with C5, eculizumab inhibits the terminal complement pathway through simultaneous blockade of the generation of the potent prothrombotic and proinflammatory molecule, C5a, and the formation of membrane attack complex initiator, C5b. Since all 3 arms of the complement cascade converge at the point of C5 activation, targeted by eculizumab, this drug may have broad potential application and is being clinically evaluated in other disorders with complement overactivation. In PNH, eculizumab has become the standard of care, proving to be a safe and effective
therapy with long-lasting effects, potentially enabling patients to become transfusion-independent and extending their survival. Eculizumab is administered as an IV infusion, and the dosing regimen prescribed for an average adult diagnosed with PNH is 600 mg weekly for the first 4 weeks, followed by 900 mg for the fifth dose 1 week later; then, 900 mg every 2 weeks thereafter. Eculizumab has been evaluated in aHUS patients through 2 prospective, open-label, single-arm studies (C08-002 and C08-003) as well as a single-arm retrospective study. In aHUS, it is prescribed for an average adult at 900 mg weekly for the first 4 weeks, followed by 1200 mg for the fifth dose 1 week later, then 1200 mg every 2 weeks thereafter. Eculizumab was generally well tolerated and no significant adverse effects were attributed to drug treatment; some adverse reactions included upper respiratory tract infections and diarrhea in prospective and retrospective studies, hypertension, headache, and leucopenia (C08-002/C08-003), and fever (C09-001R). Additional case reports suggest that eculizumab may prevent posttransplantation recurrence of aHUS, even in those patients harboring CFH/CFHR1 hybrid gene variants, who are at very high risk of recurrence. Further research is needed to determine the duration of eculizumab therapy in the context of the genetic background of aHUS cases and risk of disease relapse. The drawbacks of eculizumab therapy are associated with its potentially life-threatening side-effects, variations in response profiles, and the cost of treatment. Patients treated with eculizumab are at an increased risk of susceptibility towards life-threatening infections such as Neisseria meningitides; to prevent such infections, vaccinations and, in some cases, prophylactic antibiotic treatment is recommended. A number of serious and potentially treatment-related adverse effects were observed including pyrexia, headache, abdominal distension, viral infection, renal impairment, and anxiety. It is important to note that there is variability among individuals towards eculizumab response, and some patients may not benefit from this therapy. This is potentially a life-long therapy with a high cost of administration. The cost of eculizumab may limit its use in routine clinical practice worldwide. Therapeutic drug monitoring of eculizumab is typically not performed during treatment regimens due to the low toxicity of biologics. Measurement of therapy efficacy is usually based on clinical presentation and improvement of symptoms, although this landscape is changing, as it is recognized that patients undergoing life-long therapy with eculizumab who are in complete remission without significant evidence or pathogenic genetic variants leading to increased risk of relapse may benefit from dose de-escalation or discontinuing therapy. Pharmacodynamic studies of complement blockage may also be recommended, see ECUMP / Eculizumab Monitoring Panel, Serum for more information.

**Useful For:** Assessing the response to eculizumab therapy Assessing the need for dose escalation Evaluating the potential for dose de-escalation or discontinuation of therapy in remission states Monitoring patients who need to be above a certain eculizumab concentration in order to improve the odds of a clinical response for therapy optimization

**Interpretation:** Minimum trough therapeutic concentrations (immediately before next infusion) of eculizumab are expected to be above 35 mcg/mL for paroxysmal nocturnal hemoglobinuria (PNH) and above 50 mcg/mL for aHUS.

**Reference Values:**
- Lower limit of quantitation =5.0 mcg/mL
- >35 Therapeutic concentration for paroxysmal nocturnal hemoglobinuria (PNH)
- >50 Therapeutic concentration for atypical hemolytic uremic syndrome (aHUS)

**Clinical References:**

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**EGFRT**

**EGFR Gene, Mutation Analysis, 29 Mutation Panel, Tumor**

**Clinical Information:** Lung cancer is the leading cause of cancer-related deaths in the world. Non-small cell lung cancer (NSCLC) represents 70% to 85% of all lung cancer diagnoses. Small
molecular agents that target the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) protein are approved for the treatment of locally advanced or metastatic NSCLC as a second- or third-line regimen. Subsequently, randomized trials have suggested that targeted agents alone or combined with chemotherapy may be beneficial in maintenance and first-line settings. Because the combination of targeted therapy and standard chemotherapy leads to an increase in toxicity and cost, strategies that help to identify the individuals most likely to benefit from targeted therapies are desirable. EGFR is a growth factor receptor that is activated by the binding of specific ligands, resulting in activation of the RAS/MAPK pathway. Activation of this pathway induces a signaling cascade ultimately leading to cell proliferation. Dysregulation of the RAS/MAPK pathway is a key factor in tumor progression for many solid tumors. Targeted therapies directed to tumors harboring activating mutations within the EGFR tyrosine kinase domain (exons 18-21) have demonstrated some success in treating a subset of patients with NSCLC by preventing adenosine 5'-triphosphate (ATP)-binding at the active site. Gefitinib and erlotinib have been approved by the FDA for use in treating patients with NSCLC who previously failed to respond to the traditional platinum-based doublet chemotherapy. These 2 drugs have also recently been shown to increase progression-free and overall survival in patients who receive EGFR-tyrosine kinase inhibitor therapy as a first-line therapy for the treatment of NSCLC. Agents such as gefitinib and erlotinib, which prevent ATP binding to EGFR kinase, do not appear to have any meaningful inhibitor activity on tumors that demonstrate the presence of the specific drug-resistant EGFR mutation T790M. Therefore, current data suggest that the efficacy of EGFR-targeted therapies in NSCLC is confined to patients with tumors demonstrating the presence of EGFR-activating mutations such as L858R, L861Q, G719A/S/C, S768I or small deletions within exon 19 and the absence of the drug-resistant mutation T790M. As a result, the mutation status of EGFR can be a useful marker by which patients are selected for EGFR-targeted therapy.

**Useful For:** Identifying non-small cell lung cancers that may respond to epidermal growth factor receptor-tyrosine kinase inhibitor therapies

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.


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**Egg White IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**Egg White IgG4**

**Interpretation:** mcg/mL of IgG4 Lower Limit of Quantitation 0.15 Upper Limit of Quantitation 30.0

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Reference Values:
<0.15 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicated immunologic sensitization to the food allergen in question.

Egg White, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L  Interpretation
0            Negative
1    0.35-0.69  Equivocal
2    0.70-3.49  Positive
3    3.50-17.4  Positive
4    17.5-49.9  Strongly positive
5    50.0-99.9  Strongly positive
6 > or =100  Strongly positive Reference values apply to all ages.

Egg Whole IgE

**Interpretation:** Class IgE (kU/L) Comment 0 < 0.010 Negative 0/1 0.10 - 0.34 Equivocal/Borderline 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 17.50 - 49.99 Very High Positive 5 50.00 - 99.99 Very High Positive 6 >

**Reference Values:**
< 0.35 kU/L

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Egg Whole IgG

**Reference Values:**
< 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

---

Egg Yolk IgG

**Interpretation:** mcg/mL if IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
< 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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Egg Yolk, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
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<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Eggplant, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
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</table>

Ehrlichia Antibody Panel, Serum

Clinical Information: ANAP: Human granulocyte ehrlichiosis (HGE) is a zoonotic infection caused by a rickettsia-like agent. The infection is acquired by contact with Ixodes ticks carrying the HGE agent. The deer mouse is the animal reservoir and, overall, the epidemiology is very much like that of Lyme disease and babesiosis. HGE is most prevalent in the upper Midwest and in other areas of the United States that are endemic for Lyme disease. Since its first description in 1994, there have been approximately 50 cases of HGE described in the upper Midwest. The cellular target in HGE cases is the neutrophil. The organisms exist in membrane-lined vacuoles within the cytoplasm of infected host cells. Ehrlichial inclusions, called morulae, contain variable numbers of organisms. Single organisms, wrapped in vacuolar membranes have also been observed in the cytoplasm. Ehrlichia species occur in small electron-dense and large electron-lucent forms, but a clear life cycle has not been elucidated. Diagnosis of human ehrlichiosis has been difficult because the patient's clinical course is often mild and nonspecific, including fever, myalgias, arthralgias, and nausea. This is easily confused with other illnesses such as influenza or other tickborne zoonoses such as Lyme disease, babesiosis, and Rocky Mountain spotted fever. Clues to the diagnosis of ehrlichiosis in a patient with an acute febrile illness after tick exposure include laboratory findings of leukopenia or thrombocytopenia and elevated serum aminotransferase levels. However, these findings may also be present in patients with Lyme disease or babesiosis. EHRC Ehrlichiosis is an emerging zoonotic infection caused by obligate intracellular, gram-negative rickettsia that infects leukocytes. Human monocytic ehrlichiosis (HME) is caused by Ehrlichia chaffeensis and is transmitted by the Lone Star tick, Amblyomma americanum. The deer is believed to be the animal reservoir and most cases of HME have been reported from the southeastern and south-central region of the United States. Infectious forms are injected during tick bites and the organism enters the vascular system where it infects monocytes. It is sequestered in host-cell membrane-limited parasitophorous vacuoles known as morulae. These can be readily observed on Giemsa- or Wright-stained smears of peripheral blood from infected persons. Macrophages in organs of the reticuloendothelial system are also infected. Asexual reproduction occurs in WBCs and daughter cells are formed that are liberated upon cell rupture. Ehrlichiosis is sometimes diagnosed by observing the organisms in infected WBCs on Giemsa-stained thin blood films of smeared peripheral blood (morulae). Serology may be useful if the morulae are not seen or if the infection has cleared naturally or following treatment. Most cases of ehrlichiosis are probably subclinical or mild, but the infection can be severe and life-threatening; there is a 2% to 3% mortality rate. Fever, fatigue, malaise, headache, and other "flu-like" symptoms occur most commonly. Central nervous system involvement can result in seizures and coma. Leukopenia, thrombocytopenia, and elevated hepatic transaminases are frequent laboratory findings. Serology may also be useful in the follow-up of documented cases of ehrlichiosis or when coinfection with other tick-transmitted organisms is suspected. In selected cases, documentation of infection may be attempted by PCR methods.

Useful For: As an adjunct in the diagnosis of ehrlichiosis In seroepidemiological surveys of the prevalence of the infection in certain populations

Interpretation: A positive immunofluorescence assay (titer > or =1:64) suggests current or previous infection. In general, the higher the titer, the more likely the patient has an active infection. Four-fold rises in titer also indicate active infection. Previous episodes of ehrlichiosis may produce a positive serology although antibody levels decline significantly during the year following infection.

Reference Values:
ANAPLASMA PHAGOCYTOPHILUM

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLabs.com
Ehrlichia chaffeensis (HME) Antibody, IgG, Serum

Clinical Information: Ehrlichiosis is an emerging zoonotic infection caused by obligate intracellular, gram-negative rickettsia that infects leukocytes. Human monocytic ehrlichiosis (HME) is caused by Ehrlichia chaffeensis and is transmitted by the Lone Star tick, Amblyomma americanum. The deer is believed to be the animal reservoir and most cases of HME have been reported from the southeastern and south-central region of the United States. Infectious forms are injected during tick bites and the organism enters the vascular system where it infects monocytes. It is sequestered in host-cell membrane-limited parasitophorous vacuoles known as morulae. These can be readily observed on Giemsa- or Wright-stained smears of peripheral blood from infected persons. Macrophages in organs of the reticuloendothelial system are also infected. Asexual reproduction occurs in WBCs and daughter cells are formed that are liberated upon cell rupture. Ehrlichiosis is sometimes diagnosed by observing the organisms in infected WBCs on Giemsa-stained thin blood films of smeared peripheral blood (morulae). Serology may be useful if the morulae are not seen or if the infection has cleared naturally or following treatment. Most cases of ehrlichiosis are probably subclinical or mild, but the infection can be severe and life-threatening; there is a 2% to 3% mortality rate. Fever, fatigue, malaise, headache, and other "flu-like" symptoms occur most commonly. Central nervous system involvement can result in seizures and coma. Leukopenia, thrombocytopenia, and elevated hepatic transaminases are frequent laboratory findings. Serology may also be useful in the follow-up of documented cases of ehrlichiosis or when coinfection with other tick-transmitted organisms is suspected. In selected cases, documentation of infection may be attempted by PCR methods.

Useful For: As an adjunct in the diagnosis of ehrlichiosis In seroepidemiological surveys of the prevalence of the infection in certain populations

Interpretation: A positive immunofluorescence assay (titer \( \geq 1:64 \)) suggests current or previous infection with Ehrlichia chaffeensis. In general, the higher the titer, the more likely the patient has an active infection. Four-fold rises in titer also indicate active infection.

Reference Values:

<1:64
Reference values apply to all ages.


Ehrlichia/Anaplasma, Molecular Detection, PCR, Blood

Clinical Information: Ehrlichiosis and anaplasmosis are a group of emerging zoonotic tick-borne infections caused by Ehrlichia and Anaplasma species, respectively. These obligate intracellular, gram-negative rickettsial organisms infect leukocytes and cause a potentially serious febrile illness in humans. Human granulocytic anaplasmosis (HA) is caused by Anaplasma phagocytophilum, which is transmitted through the bite of an infected Ixodes species tick. The epidemiology of this infection in the United States is very much like that of Lyme disease (caused by Borrelia burgdorferi) and babesiosis (caused primarily by Babesia microti), which all have the same tick vector. HA is most prevalent in the...
upper Midwest and in other areas of the United States that are endemic for Lyme disease. Human monocytic ehrlichiosis (HE) is caused by Ehrlichia chaffeensis, which is transmitted by the Lone Star tick, Amblyomma americanum. Most cases of HE have been reported from the southeastern and south-central regions of the United States. E ewingii, the known cause of canine granulocytic ehrlichiosis, can occasionally cause an HE-like illness in humans. Clinical features and laboratory abnormalities are similar to those of E chaffeensis infection, and antibodies to E ewingii cross-react with current serologic assays for detection of antibodies to E chaffeensis. Most recently, Mayo Medical Laboratories detected a new species of Ehrlichia in patients with exposure to ticks in Wisconsin and Minnesota. This organism is most closely related to E muris and has therefore been referred to as the E muris-like agent or EMLA. The name E muris eauclairensis has recently been proposed after the city in which the first case was described. E muris eauclairensis causes a similar disease to ehrlichiosis due to E chaffeensis and E ewingii, and may cause more severe disease in immunocompromised hosts. Most cases of anaplasmosis and ehrlichiosis are subclinical or mild, but infection can be severe and life-threatening in some individuals. Fever, fatigue, malaise, headache, and other "flu-like" symptoms, including myalgias, arthralgias, and nausea, occur most commonly. Central nervous system involvement can result in seizures and coma. Diagnosis may be difficult since the patient's clinical course is often mild and nonspecific. This symptom complex is easily confused with other illnesses such as influenza, or other tick-borne zoonoses such as Lyme disease, babesiosis, and Rocky Mountain spotted fever. Clues to the diagnosis of ehrlichiosis in an acutely febrile patient after tick exposure include laboratory findings of leukopenia or thrombocytopenia and elevated serum aminotransferase levels. However, while these abnormal laboratory findings are frequently seen, they are not specific. Rarely, intra-granulocytic or monocytic morulae may be observed on peripheral blood smear, but this is not a reliable means of diagnosing cases of human ehrlichiosis or anaplasmosis. Definitive diagnosis is usually accomplished through PCR and serologic methods. Serologic testing is done primarily for confirmatory purposes, by demonstrating a 4-fold rise or fall in specific antibody titers to Ehrlichia species or Anaplasma antigens. There is not currently a commercially available specific serologic test for E muris eauclairensis, but cross-reactivity with the other Ehrlichia species by serology may be detected. PCR techniques allow direct detection of pathogen-specific DNA from patients' whole blood and is the preferred method for detection during the acute phase of illness. The Mayo PCR assay is capable of detecting and differentiating A phagocytophilum, E chaffeensis, E ewingii, and E muris eauclairensis. It is important to note that concurrent infection with A phagocytophilum, Borrelia burgdorferi, and Babesia microti is not uncommon as these organisms share the same Ixodes tick vector, and additional testing for these pathogens may be indicated.

**Useful For:** Evaluating patients suspected of acute anaplasmosis or ehrlichiosis

**Interpretation:** Positive results indicate presence of specific DNA from Ehrlichia chaffeensis, E ewingii, E muris eauclairensis organism, or Anaplasma phagocytophilum and support the diagnosis of ehrlichiosis or anaplasmosis. Negative results indicate absence of detectable DNA from any of these 4 pathogens in specimens, but do not exclude the presence of these organisms or active or recent disease. Since DNA of E ewingii is indistinguishable from that of E canis by this rapid PCR assay, a positive result for E ewingii/canis indicates the presence of DNA from either of these 2 organisms.

**Reference Values:**

**Negative**

**Clinical References:**

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**Elastase, Pancreatic, Serum**

**FELAS**

**90158**

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Clinical Information: Serum Elastase, also called Pancreatopeptidase, is a protease present in pancreatic secretion with the unique ability to rapidly hydrolyze elastin. Elastin is a fibrillar protein found in connective tissue. Elastin forms the elastic fibers found mostly in lungs and skin. Elastase is able to hydrolyze denatured hemoglobin, casein, fibrin, albumin and denatured but not native collagen. Elastase has been implicated in the pathogenesis of pulmonary emphysema, atherosclerosis and in the vascular injury of acute pancreatic necrosis. Elastase activity is inhibited by protease inhibitors including α1-Anti-Trypsin, α1-anti-Chymotrypsin, anti-Thrombin III, α2-Macroglobulin and β1-anti-Collagenase. Patients with thyroid dysfunction have decreased Elastase activity. Serum pancreatic levels quantify EL 1 for the diagnosis or exclusion of an acute pancreatitis or an inflammatory episode of chronic pancreatitis or gallstone induced pancreatitis.

Reference Values:
Adult Reference Ranges:
Normal pancreatic exocrine function:
Less than 3.5 ng/mL

No pediatric reference ranges available for this test.

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.
**Electrolyte and Osmolality Panel, Feces**

**Clinical Information:** The concentration of electrolytes in fecal water and their rate of excretion are dependent upon 3 factors:

- Normal daily dietary intake of electrolytes
- Passive transport from serum and other vascular spaces to equilibrate fecal osmotic pressure with vascular osmotic pressure
- Electrolyte transport into fecal water due to exogenous substances and rare toxins (e.g., cholera toxin)

Fecal osmolality is normally in equilibrium with vascular osmolality, and sodium is the major affecter of this equilibrium. Fecal osmolality is normally 2 x (sodium + potassium) unless there are exogenous factors inducing a change in composition, such as the presence of other osmotic agents (magnesium sulfate, saccharides) or drugs inducing secretions, such as phenolphthalein or bisacodyl. Osmotic diarrhea is caused by ingestion of poorly absorbed ions or sugars and can be characterized by the following:

- Stool volume typically decreased by fasting
- Fecal fluid usually has an elevated osmotic gap
- Osmotic agents such as magnesium, sorbitol, or polyethylene glycol may be the cause through the intentional or inadvertent use of laxatives
- Carbohydrate malabsorption can be differentiated from other osmotic causes by a low stool pH

Secretory diarrhea is caused by disruption of epithelial electrolyte transport and can be characterized by the following:

- Stool volume is usually unaffected by fasting
- Fecal fluid usually has elevated electrolytes (primarily sodium and chloride) and a low osmotic gap (<50 mOsm/kg)
- Common causes include bile acid malabsorption, inflammatory bowel disease, endocrine tumors, and neoplasia

Secretory agents such as anthraquinones, phenolphthalein, bisacodyl, or cholera toxin should also be considered.

**Useful For:** Workup of cases of chronic diarrhea

**Diagnosis of factitious diarrhea (where patient adds water to stool to simulate diarrhea)**

**Interpretation:**

- **Osmotic Gap:** Osmotic gap is calculated as 290 mOsm/kg -(2[Na]+2[K]). Typically, stool osmolality is similar to serum since the gastrointestinal (GI) tract does not secrete water. (1)

- An osmotic gap >50 mOsm/kg is suggestive of an osmotic component contributing to the symptoms of diarrhea. (1-3)

- Magnesium-induced diarrhea should be considered if the osmotic gap is >75 mOsm/kg and is likely if the magnesium concentration is >110 mg/dL. (1)

- An osmotic gap < or =50 mOsm/kg is suggestive of secretory causes of diarrhea. (1-3)

- A highly negative osmotic gap or a fecal sodium concentration greater than plasma or serum suggests the possibility of either sodium phosphate or sodium sulfate ingestion by the patient. (4)

- Phosphorus: Phosphorus elevation >102 mg/dL is suggestive of phosphate-induced diarrhea. (4)

- Sodium: Sodium is typically found at lower concentrations (mean 30 +/- 5 mmol/L) in patients with osmotic diarrhea caused by magnesium-containing laxatives, while typically at higher concentrations (mean 104 +/- 5 mmol/L) in patients known to be taking secretory laxatives. (5)

- Osmolality: Stool osmolality <220 mOsm/kg indicates dilution with a hypotonic fluid. (1)

- Stool osmolality >330 mOsm/kg in the absence of increased serum osmolality indicates improper storage. (1)

- Sodium and Potassium: High sodium and potassium in the absence of an osmotic gap indicate active electrolyte transport in the GI tract that may be induced by agents such as cholera toxin or hypersecretion of vasointestinal peptide. (1)

- Chloride: Markedly elevated fecal chloride concentration in infants (>60 mmol/L) and adults (>100 mmol/L) is associated with congenital and secondary chloridorrhea. (6)

- Fecal chloride may be elevated (>35 mmol/L) in phenolphthalein- or phenolphthalein plus magnesium hydroxide-induced diarrhea. (3)

- Fecal chloride may be low (<20 mmol/L) in sodium sulfate-induced diarrhea. (3)

**Reference Values:**

No established reference values

**Clinical References:**

Electrolyte Panel, Serum

**Clinical Information:** The electrolyte panel is ordered to identify electrolyte, fluid, or pH imbalance. Electrolyte concentrations are evaluated to assist in investigating conditions that cause electrolyte imbalances such as dehydration, kidney disease, lung diseases, or heart conditions. Repeat testing of the electrolyte or its components may be used to monitor the patient’s response to treatment of any condition that may be causing the electrolyte, fluid, or pH imbalance. Electrolyte and acid-base imbalances can often be indicative of many acute and chronic illnesses. For this reason, the electrolyte panel is often used in the hospital and emergency settings to evaluate patients.

**Useful For:** Identifying a suspected imbalance in electrolytes or acid/base imbalance

**Interpretation:** With an imbalance of a single electrolyte, such as sodium or potassium, repeat testing may be ordered of that particular electrolyte, can be used to monitor the imbalance until remedied. With an acid-base imbalance, blood gases may be ordered, which will measure the oxygen, carbon dioxide, and pH levels in the arterial blood. These tests assist in evaluating the acuteness of the imbalance and monitoring the response to treatment.

**Reference Values:**

**SODIUM**
- <1 year: not established
- > or =1 year: 135-145 mmol/L

**POTASSIUM**
- <1 year: not established
- > or =1 year: 3.6-5.2 mmol/L

**CHLORIDE**
- <1 year: not established
- 1-17 years: 102-112 mmol/L
- > or =18 years: 98-107 mmol/L

**BICARBONATE**
- Males
  - <1 year: not established
  - 1-2 years: 17-25 mmol/L
  - 3 years: 18-26 mmol/L
  - 4-5 years: 19-27 mmol/L
  - 6-7 years: 20-28 mmol/L
  - 8-17 years: 21-29 mmol/L
  - > or =18 years: 22-29 mmol/L
- Females
  - <1 year: not established
  - 1-3 years: 18-25 mmol/L
  - 4-5 years: 19-26 mmol/L
  - 6-7 years: 20-27 mmol/L
  - 8-9 years: 21-28 mmol/L

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> or =10 years: 22-29 mmol/L

ANION GAP
<7 years: not established
> or =7 years: 7-15


**Electron Microscopy**

**Clinical Information:** Crucial diagnostic information for the study of human disease may be provided by transmission and scanning electron microscopy. Often information of a confirmatory nature or of educational value to the clinician and pathologist can be obtained by this procedure. In recent years, the technology involved in electron microscopy has progressed to the point where methods have become standardized and the instrumentation routine. The electron microscope is a fundamental tool in medical diagnostic and cellular pathobiological investigations, because it is at this instrument's level of resolution that most structural correlations with function and metabolism are visible.

**Useful For:** Identifying tumor Diagnosing medical disorders such as storage diseases, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and primary ciliary dyskinesia

**Interpretation:** The images and case histories are correlated and interpreted by a pathologist who is an expert in the field of the suspected diagnoses. Results will be provided by telephone. If requested, representative images showing diagnostic features will be sent.

**Reference Values:**
An interpretive report will be provided.


**Electrophoresis, Protein, 24 Hour, Urine**

**Clinical Information:** Urine proteins can be grouped into 5 fractions by protein electrophoresis:
- Albumin
- Alpha-1
- Alpha-2
- Beta-globulin
- Gamma globulin
The urine total protein concentration, the electrophoretic pattern, and the presence of a monoclonal immunoglobulin light chain may be characteristic of monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, and light chain deposition disease. The following algorithms are available in Special Instructions:
- Laboratory Approach to the Diagnosis of Amyloidosis
- Laboratory Screening Tests for Suspected Multiple Myeloma

**Useful For:** Monitoring patients with monoclonal gammopathies

**Interpretation:** A characteristic monoclonal band (M-spike) is often found in the urine of patients with monoclonal gammopathies. The initial identification of an M-spike or an area of restricted migration should be followed by immunofixation to identify the immunoglobulin heavy chain and/or light chain. Immunoglobulin heavy chain fragments as well as free light chains may be seen in the urine of patients with monoclonal gammopathies. The presence of a monoclonal light chain M-spike of greater than 1 g/24 hours is consistent with a diagnosis of multiple myeloma or macroglobulinemia. The presence of a small amount of monoclonal light chain and proteinuria (total protein >3 g/24 hours) that is predominantly albumin is consistent with amyloidosis (AL) or light chain deposition disease (LCDD). Because patients with AL and LCDD may have elevated urinary protein without an identifiable M-spike, urine protein electrophoresis is not considered an adequate screen for these disorders and immunofixation is also recommended.
Reference Values:
PROTEIN, TOTAL
<229 mg/24 hours

Reference values have not been established for patients <18 years of age.

Reference value applies to 24-hour collection.

ELECTROPHORESIS, PROTEIN
The following fractions, if present, will be reported as a percent of the protein, total:
Albumin
Alpha-1-globulin
Alpha-2-globulin
Beta-globulin
Gamma-globulin

Clinical References:

Electrophoresis, Protein, Body Fluid
Clinical Information: Body fluid proteins can be grouped into 5 fractions by protein electrophoresis (PEL): -Albumin -Alpha-1 Globulin -Alpha-2 Globulin -Beta Globulin -Gamma Globulin The concentration of these fractions and the electrophoretic pattern may identify abnormalities in the levels of the various fractions. Protein electrophoresis alone is not considered an adequate screening for body fluid or serum monoclonal gammopathies.

Useful For: Monitoring patient's body fluid proteins Aiding in the diagnosis of monoclonal gammopathies, when used in conjunction with immunofixation of the patient's serum Detecting oligoclonal banding in spinal fluid (the preferred test for detecting oligoclonal bands in spinal fluid is OLIG / Oligoclonal Banding, Serum and Spinal Fluid)

Interpretation: Monoclonal gammopathies: A characteristic monoclonal band (M-spike) is often found in the gamma-globulin region and more rarely in the beta or alpha-2 regions. The finding of a M-spike, restricted migration, or hypogammaglobulinemic body fluid protein electrophoresis pattern is suggestive of a possible monoclonal protein and should be followed by a MPSS / Monoclonal Protein Study, Serum using the patientâ€™s serum, which includes immunofixation to identify the immunoglobulin heavy chain and/or light chain.

Reference Values: Not applicable


Electrophoresis, Protein, Random, Urine
Clinical Information: Urine proteins can be grouped into 5 fractions by protein electrophoresis:
-Albumin -Alpha-1 -Alpha-2 -Beta-globulin -Gamma globulin The urine total protein concentration, the electrophoretic pattern, and the presence of a monoclonal immunoglobulin light chain may be characteristic of monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis,
and light-chain deposition disease. The following algorithms are available in Special Instructions:

- Laboratory Approach to the Diagnosis of Amyloidosis
- Laboratory Screening Tests for Suspected Multiple Myeloma

**Useful For:** Identifying monoclonal gammopathies using random urine specimens

**Interpretation:** A characteristic monoclonal band (M-spike) is often found in the urine of patients with monoclonal gammopathies. The initial identification of an M-spike or an area of restricted migration should be followed by immunofixation to identify the immunoglobulin heavy chain and/or light chain. Immunoglobulin heavy chain fragments as well as free light chains may be seen in the urine of patients with monoclonal gammopathies. The presence of a monoclonal light chain M-spike of greater than 1 g/24 hours is consistent with a diagnosis of multiple myeloma or macroglobulinemia. The presence of a small amount of monoclonal light chain and proteinuria (total protein >3 g/24 hours) that is predominantly albumin is consistent with primary systemic amyloidosis (AL) and light-chain deposition disease (LCDD). Because patients with AL and LCDD may have elevated urinary protein without an identifiable M-spike, urine protein electrophoresis is not considered an adequate screen for these disorders and immunofixation is also recommended.

**Reference Values:**

**PROTEIN, TOTAL**

No reference values apply to random urine.

**ELECTROPHORESIS, PROTEIN**

The following fractions, if present, will be reported as a percent of the total protein:

- Albumin
- Alpha-1-globulin
- Alpha-2-globulin
- Beta-globulin
- Gamma-globulin

No reference values apply to random urines.

**Clinical References:**


**Electrophoresis, Protein, Serum**

**Clinical Information:** Serum proteins can be grouped into 5 fractions by protein electrophoresis: - Albumin, which represents almost two-thirds of the total serum protein - Alpha-1, composed primarily of alpha-1-antitrypsin (A1AT), an alpha-1-acid glycoprotein - Alpha-2, composed primarily of alpha-2-macroglobulin and haptoglobin - Beta, composed primarily of transferrin and C3 - Gamma, composed primarily of immunoglobulins The concentration of these fractions and the electrophoretic pattern may be characteristic of diseases such as monoclonal gammopathies, A1AT deficiency disease, nephrotic syndrome, and inflammatory processes associated with infection, liver disease, and autoimmune diseases.

**Useful For:** Monitoring patients with monoclonal gammopathies Diagnosis of monoclonal gammopathies, when used in conjunction with immunofixation Protein electrophoresis alone is not considered an adequate screen for monoclonal gammopathies

**Interpretation:** Monoclonal Gammopathies: - A characteristic monoclonal band (M-spike) is often found on protein electrophoresis (PEL) in the gamma-globulin region and more rarely in the beta or alpha-2 regions. The finding of a M-spike, restricted migration, or hypogammaglobulinemic PEL pattern is suggestive of a possible monoclonal protein and should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine, which includes immunofixation (IF), to identify the immunoglobulin
heavy chain and/or light chain. - A monoclonal IgG or IgA greater than 3 g/dL is consistent with multiple myeloma (MM). - A monoclonal IgG or IgA less than 3 g/dL may be consistent with monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis, early or treated myeloma, as well as a number of other monoclonal gammopathies. - A monoclonal IgM greater than 3 g/dL is consistent with macroglobulinemia. - The initial identification of a serum M-spike greater than 1.5 g/dL on PEL should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. - The initial identification of an IgM, IgA, or IgG M-spike greater than 4 g/dL, greater than 5 g/dL, and greater than 6 g/dL, respectively, should be followed by VISCS / Viscosity, Serum. - After the initial identification of an M-spike, quantitation of the M-spike on follow-up PEL can be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the beta region (most commonly an IgA or an IgM) quantitative immunoglobulin levels may be more a useful tool to follow the monoclonal protein level than PEL. A decrease or increase of the M-spike that is greater than 0.5 g/dL is considered a significant change. - Patients suspected of having a monoclonal gammopathy may have normal serum PEL patterns. Approximately 11% of patients with MM have a completely normal serum PEL, with the monoclonal protein only identified by IF. Approximately 8% of MM patients have hypogammaglobulinemia without a quantifiable M-spike on PEL but identified by IF. Accordingly, a normal serum PEL does not rule out the disease and should not be used to screen for the disorder. The MPSS / Monoclonal Protein Study, Serum, which includes immunofixation, and FLCP / Immunoglobulin Free Light Chains, Serum should be done to screen if the clinical suspicion is high. Other Abnormal PEL Findings: - A qualitatively normal but elevated gamma fraction (polyclonal hypergammaglobulinemia) is consistent with infection, liver disease, or autoimmune disease. - A depressed gamma fraction (hypogammaglobulinemia) is consistent with immune deficiency and can also be associated with primary amyloidosis or nephrotic syndrome. - A decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.1 g/dL), and decreased gamma fraction (<1 g/dL) is consistent with nephrotic syndrome, and when seen in an adult older than 40 years, should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. - In the hereditary deficiency of a protein (eg, agammaglobulinemia, alpha-1-antitrypsin (A1AT) deficiency, hypoalbuminemia), the affected fraction is faint or absent. - An absent alpha-1 fraction is consistent with A1AT deficiency disease and should be followed by a quantitative A1AT assay (AAT / Alpha-1- Antitrypsin, Serum).

Reference Values:
PROTEIN, TOTAL
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients that are <12 months of age.

PROTEIN ELECTROPHORESIS
Albumin: 3.4-4.7 g/dL
Alpha-1-globulin: 0.1-0.3 g/dL
Alpha-2-globulin: 0.6-1.0 g/dL
Beta-globulin: 0.7-1.2 g/dL
Gamma-globulin: 0.6-1.6 g/dL
An interpretive comment is provided with the report.


SPEP 97408

Electrophoresis, Protein, Serum

Clinical Information: This profile includes both total protein and protein electrophoresis. The serum proteins can be grouped into 5 fractions by protein electrophoresis: -Albumin, which represents almost two-thirds of the total serum protein -Alpha-1, composed primarily of alpha-1-antitrypsin (A1AT), an alpha-1-acid glycoprotein -Alpha-2, composed primarily of alpha-2-macroglobulin and haptoglobin -Beta, composed primarily of transferrin and C3 -Gamma, composed primarily of immunoglobulins The concentration of these fractions and the electrophoretic pattern may be characteristic of diseases such as monoclonal gammopathies, A1AT deficiency disease, nephrotic syndrome, and inflammatory processes associated with infection, liver disease, and autoimmune diseases.
Useful For: Screening patients with suspected monoclonal gammopathies Diagnosis of monoclonal gammopathies, when used in conjunction with matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) and free light chains

Interpretation: Monoclonal Gammopathies: A characteristic monoclonal band (M-spike) is often found on serum protein electrophoresis (SPE) in the gamma-globulin region and, more rarely, in the beta or alpha-2 regions. The finding of a M-spike, restricted migration, or hypogammaglobulinemic SPE pattern is suggestive of a possible monoclonal protein and should be confirmed by immunoaffinity-purification matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) to identify any immunoglobulin heavy or light chains. A MPSU / Monoclonal Protein Study, Urine is suggested for first-time M-spike patients to assess for renal disease that can be associated with an M-spike. -A monoclonal IgG or IgA greater than 3 g/dL is consistent with multiple myeloma (MM). -A monoclonal IgG or IgA less than 3 g/dL may be consistent with monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis, early or treated myeloma, as well as a number of other monoclonal gammopathies. -A monoclonal IgM greater than 3 g/dL is consistent with macroglobulinemia. -The initial identification of a serum M-spike greater than 1.5 g/dL on SPE should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -The initial identification of an IgM, IgA, or IgG M-spike greater than 4 g/dL, greater than 5 g/dL, and greater than 6 g/dL, respectively, should be followed by VISCS / Viscosity, Serum. After the initial identification of an M-spike, quantitation of the M-spike on follow-up SPE can be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the beta region (most commonly an IgA or an IgM) quantitative immunoglobulin levels may be more a useful tool to follow the monoclonal protein level than SPE. A decrease or increase of the M-spike that is greater than 0.5 g/dL is considered a significant change. Patients suspected of having a monoclonal gammopathy may have normal serum SPE patterns. Approximately 11% of patients with MM have a completely normal serum SPE, with the monoclonal protein only identified by MALDI-TOF MS. Approximately 8% of MM patients have hypogammaglobulinemia without a quantifiable M-spike on SPE but identified by MALDI-TOF MS. Accordingly, a normal serum SPE does not rule out the disease and should not be used to screen for the disorder. The SMOGA / Monoclonal Gammopathy Screen, Serum, which includes MALDI-TOF MS, and serum free light chains, conforms to the International Myeloma Working Group (IMWG) guidelines for screening and should be performed if there is clinical suspicion. Other Abnormal SPE Findings: -A qualitatively normal but elevated gamma fraction (polyclonal hypergammaglobulinemia) is consistent with infection, liver disease, or autoimmune disease. -A decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.1 g/dL), and decreased gamma fraction (<1 g/dL) is consistent with nephrotic syndrome, and when seen in an adult older than 40 years, should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -In the hereditary deficiency of a protein (eg, agammaglobulinemia, alpha-1-antitrypsin [A1AT] deficiency, hypoalbuminemia), the affected fraction is faint or absent. -An absent alpha-1 fraction is consistent with A1AT deficiency disease and should be followed by a quantitative A1AT assay (AAT / Alpha-1- Antitrypsin, Serum).

Reference Values:
TOTAL PROTEIN
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients that are <12 months of age.

PROTEIN ELECTROPHORESIS
Albumin: 3.4-4.7 g/dL
Alpha-1-globulin: 0.1-0.3 g/dL
Alpha-2-globulin: 0.6-1.0 g/dL
Beta-globulin: 0.7-1.2 g/dL
Gamma-globulin: 0.6-1.6 g/dL
An interpretive comment is provided with the report.
Reference values have not been established for patients that are <16 years of age.

Elm, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


EMR 113366

EM, Renal Biopsy (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.
Emery-Dreifuss Panel (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

Encainide (Enkaidr), ODE and MODE

Reference Values:
Encainide:
Reference Range: 15 - 100 ng/mL

O-Demethylencaainide (ODE):
Reference Range: 100 - 300 ng/mL

3-Methoxy-ODE (MODE):
Reference Range: 60 - 300 ng/mL

10% of patients do not form therapeutic concentrations of the active metabolites, ODE and MODE. In these patients the recommended range for the encainide concentration is 300 - 1200 ng/mL.

Encephalopathy, Autoimmune Evaluation, Serum

Clinical Information: Autoimmune encephalopathies extend beyond the classically recognized clinical and radiological spectrum of "limbic encephalitis." They encompass a diversity of neurological presentations with subacute or insidious onset, including confusional states, psychosis, delirium, memory loss, hallucinations, movement disorders, sensory or motor complaints, seizures, dyssomnias, ataxias, eye movement problems, nausea, vomiting, inappropriate antidiuresis, coma, dysautonomias, or hypoventilation. A diagnosis of autoimmune encephalopathy should be suspected on the basis of clinical course, coexisting autoimmune disorder (eg, thyroiditis, diabetes), serological evidence of autoimmunity, spinal fluid evidence of intrathecal inflammation, neuroimaging or electroencephalographic abnormalities, and favorable response to trial of immunotherapy. Detection of 1 or more neural autoantibodies aids the diagnosis of autoimmune encephalopathy and may guide a search for cancer. Pertinent autoantibody specificities include: 1) neurotransmitter receptors and ion channels such as neuronal voltage-gated potassium channels (and interacting synaptic and axonal proteins, LGI1 and CASPR2), ionotropic glutamate receptors (NMDA and AMPA), metabotropic GABA-B receptors; 2) enzymes, signaling molecules, and RNA-regulatory proteins in the cytoplasm and nucleus of neurons (GAD65, CRMP-5, ANNA-1, and ANNA-2). Importantly, autoimmune encephalopathies are reversible. Misdiagnosis as a progressive (currently irreversible) neurodegenerative condition is not uncommon and has devastating consequences for the patient. Clinicians must consider the possibility of an autoimmune etiology in the differential diagnoses of encephalopathy. For example, a potentially reversible disorder justifies a trial of immunotherapy for the detection of neural autoantibodies in patients presenting with symptoms of personality change, executive dysfunction, and psychiatric manifestations. A triad of clues helps to identifying patients with an autoimmune encephalopathy: 1) clinical presentation (subacute symptoms onset rapidly progressive course and fluctuating symptoms) and radiological findings consistent with inflammation, 2) detection of neural autoantibodies in serum or cerebrospinal fluid (CSF), and 3) favorable response to a trial of immunotherapy. Detection of neural autoantibodies in serum or CSF informs the physician of a likely autoimmune etiology, and may heighten suspicion for a paraneoplastic basis and guide the search for cancer. Neurological accompaniments of neural autoantibodies are generally not syndromic, but diverse and multifocal. For example, neuronal voltage-gated potassium channel (VGKC)-complex antibodies were initially considered specific for autoimmune limbic encephalitis or disorders of peripheral nerve hyperexcitability. However, more diverse presentations are now recognized, including rapidly
progressive cognitive decline mimicking frontotemporal dementia and Creutzfeldt-Jakob disease. Comprehensive antibody testing is more informative than selective testing for 1 or 2 neural antibodies. Some antibodies strongly predict an underlying cancer. For example; small-cell lung carcinoma (antineuronal nuclear antibody-type 1, ANNA-1; collapsin response-mediator protein-5 neuronal, CRMP-5-IgG), ovarian teratoma (N-methyl-D-aspartate receptor, NMDA-R), and thymoma (CRMP-5 IgG). An individual patient's profile autoantibody may be informative for a specific cancer type. For example, detection of muscle acetylcholine receptor (AChR) binding, alpha 3 ganglionic AchR, and CRMP 5 IgG in a patient presenting with encephalopathy suggests thymoma. When an associated tumor is found, its resection or ablation optimizes the neurological outcome. Testing of CSF for autoantibodies is particularly helpful when serum testing is negative. Simultaneous testing of serum and CSF is recommended for NMDA-R antibody, because CSF is usually more informative.

Useful For: Evaluating new onset encephalopathy (noninfectious or metabolic) comprising confusional states, psychosis, delirium, memory loss, hallucinations, movement disorders, sensory or motor complaints, seizures, dyssomnias, ataxias, nausea, vomiting, inappropriate antidiuresis, coma, dysautonomias, or hypoventilation in serum specimens

Interpretation: Neuronal, glial, and muscle autoantibodies are valuable serological markers of autoimmune encephalopathy and a patient's immune response to cancer. These autoantibodies are usually accompanied by subacute neurological symptoms and signs are not found in healthy subjects. It is not uncommon for more than 1 of the following autoantibody specificities to be detected in patients with an autoimmune encephalopathy: - Plasma membrane autoantibodies: voltage-gated potassium channel complex, N-Methyl-D-aspartate (NMDA) receptor; 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid (AMPA) receptor; gamma-amino butyric acid (GABA-B) receptor; neuronal Ach receptor. These are all potential effectors of neurological dysfunction - Neuronal nuclear autoantibodies, type 1 (ANNA-1), type 2 (ANNA-2), or type 3 (ANNA-3). - Neuronal or muscle cytoplasmic antibodies: amphiphysin, Purkinje cell antibodies (PCA-1) and PCA-2, CRMP-5, GA65, or striational.

Reference Values:

**NEURONAL NUCLEAR ANTIBODIES**
Antineuronal Nuclear Ab, Type 1 (ANNA-1) <1:240
Antineuronal Nuclear Ab, Type 2 (ANNA-2) <1:240
Antineuronal Nuclear Ab, Type 3 (ANNA-3) <1:240
Anti-Glial/Neuronal Nuclear Ab, Type 1 (AGNA-1) <1:240

**NEURONAL AND MUSCLE CYTOPLASMIC ANTIBODIES**
Purkinje Cell Cytoplasmic Ab, Type 1 (PCA-1) <1:240
Purkinje Cell Cytoplasmic Ab, Type 2 (PCA-2) <1:240
Purkinje Cell Cytoplasmic Ab, Type Tr (PCA-Tr) <1:240
Amphiphysin Antibody <1:240
CRMP-5-IgG <1:240

WESTERN BLOT
Paraneoplastic Western Blot
Negative
CRMP-5-IgG Western Blot
Negative
Amphiphysin Western Blot
Negative

ISLET CELL ANTIBODIES
Glutamic Acid Decarboxylase (GAD65) Antibody
< or =0.02 nmol/L

CATION CHANNEL ANTIBODIES
N-Type Calcium Channel Antibody
< or =0.03 nmol/L
P/Q-Type Calcium Channel Antibody
< or =0.02 nmol/L
AChR Ganglionic Neuronal Antibody
< or =0.02 nmol/L
Neuronal VGKC Autoantibody
< or =0.02 nmol/L

ACHR RECEPTOR ANTIBODIES
ACh Receptor (Muscle) Binding Antibody
< or =0.02 nmol/L

N-Methyl-D-aspartate receptor (NMDA-R)
CBA: Negative
IFA: <1:120
2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid receptor (AMPA-R)
CBA: Negative
IFA: <1:120
Gamma-Amino Butyric acid-type B receptor (GABA-B-R)
CBA: Negative
IFA: <1:120
LGI1-IgG CBA, S: Negative
CASPR2-IgG CBA, S: Negative

Neuromyelitis Optica (NMO)/Aquaporin-4-IgG FACS Assay, S
Negative

Lucchinetti CF, Kimmel DW, Lennon VA: Paraneoplastic and oncological profiles of patients
Yoshikawa H, Ahlskog JE, et al: Glutamic acid decarboxylase autoimmunity with brainstem,
extrapyramidal and spinal cord dysfunction. Mayo Clin Proc 2006;81:1207-1214 4. Lancaster E,
Martinez-Hernandez E, Dalmau J: Encephalitis and antibodies to synaptic and neuronal cell surface
and CASPR2 potassium channel complex autoantibody subtyping. JAMA Neurol 2013;70(2):229-234
hypoventilation. A diagnosis of autoimmune encephalopathy should be suspected on the basis of clinical course, coexisting autoimmune disorder (eg, thyroiditis, diabetes), serological evidence of autoimmunity, spinal fluid evidence of intrathecal inflammation, neuroimaging or electroencephalographic abnormalities, and favorable response to trial of immunotherapy. Detection of 1 or more neural autoantibodies aids the diagnosis of autoimmune encephalopathy and may guide a search for cancer. Pertinent autoantibody specificities include: 1) neurotransmitter receptors and ion channels such as neuronal voltage-gated potassium channels (and interacting synaptic and axonal proteins, LGI1 and CASPR2), ionotropic glutamate receptors (NMDA and AMPA), metabotropic GABA-B receptors; 2) enzymes, signaling molecules and RNA-regulatory proteins in the cytoplasm and nucleus of neurons (GAD65, CRMP-5, ANNA-1, and ANNA-2). Importantly, autoimmune encephalopathies are reversible. Misdiagnosis as a progressive (currently irreversible) neurodegenerative condition is not uncommon and has devastating consequences for the patient. Clinicians must consider the possibility of an autoimmune etiology in the differential diagnoses of encephalopathy. For example, a potentially reversible disorder justifies a trial of immunotherapy for the detection of neural autoantibodies in patients presenting with symptoms of personality change, executive dysfunction, and psychiatric manifestations. A triad of clues helps to identify patients with an autoimmune encephalopathy: 1) clinical presentation (subacute symptoms onset rapidly progressive course and fluctuating symptoms) and radiological findings consistent with inflammation, 2) detection of neural autoantibodies in serum or cerebral spinal fluid (CSF), and 3) favorable response to a trial of immunotherapy. Detection of neural autoantibodies in serum or CSF informs the physician of a likely autoimmune etiology, and may heighten suspicion for a paraneoplastic basis and guide the search for cancer. Neurological accompaniments of neural autoantibodies are generally not syndromic, but diverse and multifocal. For example, neuronal voltage-gated potassium channel (VGKC)-complex antibodies were initially considered specific for autoimmune limbic encephalitis or disorders of peripheral nerve hyperexcitability. However, more diverse presentations are now recognized, including rapidly progressive cognitive decline mimicking frontotemporal dementia and Creutzfeld-Jakob disease. Comprehensive antibody testing is more informative than selective testing for 1 or 2 neural antibodies. Some antibodies strongly predict an underlying cancer. For example; small-cell lung carcinoma (antineuronal nuclear antibody-type 1: ANNA-1; collapsin response-mediator protein-5 neuronal: CRMP-5-IgG), ovarian teratoma (N-methyl-D-aspartate receptor: NMDA-R), and thymoma (CRMP-5 IgG). An individual patient's profile autoantibody may be informative for a specific cancer type. For example, detection of muscle acetylcholine receptor (AChR) binding, alpha 3 ganglionic AChR, and CRMP-5 IgG in a patient presenting with encephalopathy suggests thymoma. When an associated tumor is found, its resection or ablation optimizes the neurological outcome. Testing of CSF for autoantibodies is particularly helpful when serum testing is negative. Simultaneous testing of serum and CSF is recommended for NMDA-R antibody, because CSF is usually more informative.

**Useful For:** Evaluating new onset encephalopathy (noninfectious or metabolic) comprising confusional states, psychosis, delirium, memory loss, hallucinations, movement disorders, sensory or motor complaints, seizures, dyssomnias, ataxias, nausea, vomiting, inappropriate antidiuresis, coma, dysautonomias, or hypoventilation in spinal fluid specimens The following accompaniments should increase of suspicion for autoimmune encephalopathy: -Headache -Autoimmune stigmata (personal or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, poliosis [premature graying], myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus) -History of cancer -Smoking history (20+ pack years) or other cancer risk factors -Inflammatory cerebral spinal fluid (or isolated protein elevation) -Neuroimaging signs suggesting inflammation Evaluating limbic encephalitis (noninfectious) Directing a focused search for cancer Investigating encephalopathy appearing in the course or wake of cancer therapy and not explainable by metastasis or drug effect

**Interpretation:** Neuronal, glial, and muscle autoantibodies are valuable serological markers of autoimmune encephalopathy and of a patient's immune response to cancer. These autoantibodies are usually accompanied by subacute neurological symptoms and signs are not found in healthy subjects. It is not uncommon for more than 1 of the following autoantibody specificities to be detected in patients with an autoimmune encephalopathy: -Plasma membrane autoantibodies: These are all potential effectors of neurological dysfunction: neuronal voltage-gated potassium channel (VGKC)-complex, N-methyl-D-aspartate (NMDA) receptor; 2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl) propanoic acid (AMPA) receptor; gamma-aminobutyric acid (GABA-B) receptor; neuronal ACh receptor. -Neuronal nuclear autoantibodies: type 1 (ANNA-1), type 2 (ANNA-2), or type 3 (ANNA-3) -Neuronal or muscle...
cytoplasmic antibodies: amphiphysin, Purkinje cell antibodies (PCA-1 and PCA-2), CRMP-5, GA65, or striational.

**Reference Values:**

**NEURONAL NUCLEAR ANTIBODIES**
- Antineuronal Nuclear Antibody-Type 1 (ANNA-1) <1:2
- Antineuronal Nuclear Antibody-Type 2 (ANNA-2) <1:2
- Antineuronal Nuclear Antibody-Type 3 (ANNA-3) <1:2
- Anti-Glial/Neuronal Nuclear Antibody-Type 1 (AGNA-1) <1:2

**NEURONAL AND MUSCLE CYTOPLASMIC ANTIBODIES**
- Purkinje Cell Cytoplasmic Antibody, Type 1 (PCA-1) <1:2
- Purkinje Cell Cytoplasmic Antibody, Type 2 (PCA-2) <1:2
- Purkinje Cell Cytoplasmic Antibody, Type TR (PCA-TR) <1:2
- Amphiphysin Antibody <1:2
- Collapsin Response-Mediator Protein-5 Neuronal (CRMP-5-IGG) <1:2

**ISLET CELL ANTIBODIES**
- Glutamic Acid Decarboxylase (GAD65) Antibody Assay < or =0.02 nmol/L
- AMPA-RECEPTOR ANTIBODY BY CBA
  - CBA: Negative
  - IFA: <1:2
- GABA-B-RECEPTOR ANTIBODY BY CBA
  - CBA: Negative
  - IFA: <1:2
- NMDA-RECEPTOR ANTIBODY BY CBA
  - CBA: Negative
  - IFA: <1:2
- LGII-IgG CBA: Negative
- CASPR2-IgG CBA: Negative

- Neuronal Voltage-Gated Potassium Channel-Complex Autoantibody < or =0.02 nmol/L
- WESTERN BLOT
  - Paraneoplastic Autoantibody, Western Blot Confirmation Negative
  - Collapsin Response-Mediator Protein-5-Igg (CRMP-5-Igg) Western Blot Negative
  - Amphiphysin Antibody Western Blot Negative

ESTUF
35851

Endometrial Stromal Tumors (EST), 7p15 (JAZF1), 6p21.32 (PHF1), 17p13.3 (YWHAE) Rearrangement, FISH, Tissue

Clinical Information: Endometrial stromal tumors (EST) arise from the uterus and include the benign endometrial stromal nodule (ESN) and infiltrative endometrial stromal sarcoma (ESS). These tumors are characterized by a translocation that fuses JAZF1 at 7p15 to JJA1 at 17q21 or a variant 6:7 translocation involving JAZF1 and PHF1. Published literature employing FISH and reverse transcription PCR (RT-PCR) suggests rearrangement of JAZF1 occurs in approximately 76% of ESN and approximately 58% of ESS. JAZF1 is not generally considered to be involved in the genetic mechanism of the high-grade undifferentiated endometrial sarcoma (UES), although rarely some cases of UES are positive for JAZF1, which may reflect the presence of an ESS component. For PHF1 disruption, a study of 94 EST demonstrated the following: -PHF1/JAZF1 fusion in 4 primary ESS - PHF1/EPC1 fusion in 2 primary ESS and 1 extrauterine ESS - PHF1 rearrangement without a known partner in 6 primary or metastatic ESS and 1 extrauterine ESS JAZF1/JJA1, PHF1/JAZF1 and PHF1/EPC1 fusions were mutually exclusive in individual patients.(4) No rearrangement of PHF1 was found in ESN, UES, or non-EST tumors in the differential diagnosis. These results indicate that PHF1 can rearrange with both known and unknown partners in addition to JAZF1 and is potentially specific for ESS. In high-grade ESS, a recurrent t(10;17)(q22;p13) resulting in fusion of YWHAE (also called 14-3-3epsilon at 17p13.3 with either FAM22A or FAM22B was identified. In contrast, JAZF1 rearrangements are typically observed in low-grade ESS. JAZF1 and YWHAE rearrangements are mutually exclusive and have distinct gene expression profiles. YWHAE rearrangement is potentially specific for high-grade ESS as no YWHAE disruption has been reported in other uterine or nonuterine mesenchymal tumors. The clinical utility of identifying JAZF1 rearrangement is mainly to address the differential diagnostic dilemma that occurs when ESS are present as metastatic lesions or exhibit variant morphology. In JAZF1-negative EST cases, reflex genetic analysis to identify PHF1 or YWHAE rearrangement increases the diagnostic sensitivity for EST. In addition, confirmation of YWHAE rearrangement may have prognostic implications as YWHAE defines a distinct, clinically more aggressive and histologically higher grade subgroup of ESS compared to those with JAZF1 rearrangements.

Useful For: Supporting the diagnosis of endometrial stromal tumors when used in conjunction with an anatomic pathology consultation

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for any given probe. Detection of an abnormal clone likely indicates a diagnosis of an endometrial stromal tumor of various subtypes. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.


Endomysial (EMA) IgG antibody titer

**Interpretation:** Endomysial (EMA) antibody (IgG) screen: Positive findings of IgA class endomysial antibodies (IgA EMA) is consistent with dermatitis herpetiformis and/or celiac disease. If the disease is controlled by a gluten free diet, these antibodies will disappear. Repeat titrations for these IgA EMA can be used to monitor strict adherence to a gluten free diet. Negative results for IgA class endomysial antibodies are not consistent with a diagnosis of dermatitis herpetiformis or celiac disease. The sensitivity of this test on the average is about 70% in dermatitis herpetiformis and almost 100% in untreated Celiac Disease. Endomysial (EMA) antibody (IgG) titer: IgG-EMA is generally only significant in those individuals who are IgA deficient and thus cannot produce IgA-EMA.

**Reference Values:**
- Negative: <1:2.5 titer
- Positive: > or = 1:2.5 titer

**Endomysial (IgA), Titer, Serum**

**Reference Values:**
Only orderable as a reflex. For more information see EMA / Endomysial Antibodies (IgA), Serum.

Negative

**Endomysial Antibodies (IgA), Serum**

**Clinical Information:** Circulating IgA endomysial antibodies are present in 70% to 80% of patients with dermatitis herpetiformis or celiac disease, and in nearly all such patients who have high grade gluten-sensitive enteropathy and are not adhering to a gluten-free diet. For your convenience, we recommend utilizing cascade testing for celiac disease. Cascade testing ensures that testing proceeds in an algorithmic fashion. The following cascades are available; select the appropriate one for your specific patient situation. Algorithms for the cascade tests are available in Special Instructions.

- CDCOM / Celiac Disease Comprehensive Cascade: complete testing including HLA DQ - CDSP / Celiac Disease Serology Cascade: complete testing excluding HLA DQ - CDGF / Celiac Disease Gluten-Free Cascade: for patients already adhering to a gluten-free diet To order individual tests, see Celiac Disease Diagnostic Testing Algorithm in Special Instructions.

**Useful For:** Diagnosis of dermatitis herpetiformis and celiac disease Monitoring adherence to gluten-free diet in patients with dermatitis herpetiformis and celiac disease Because of the high specificity of endomysial antibodies for celiac disease, the test may obviate the need for multiple small bowel biopsies to verify the diagnosis. This may be particularly advantageous in the pediatric population, including the evaluation of children with failure to thrive.

**Interpretation:** The finding of IgA-endomysial antibodies (EMA) is highly specific for dermatitis herpetiformis or celiac disease. The titer of IgA-EMA generally correlates with the severity of gluten-sensitive enteropathy. If patients strictly adhere to a gluten-free diet, the titer of IgA-EMA should begin to decrease within 6 to 12 months of onset of dietary therapy. Occasionally, the staining results...
cannot be reliably interpreted as positive or negative because of strong smooth muscle staining, weak EMA staining or other factors; in this case, the results will be recorded as "indeterminate." In this setting, further testing with measurement of TTGA / Tissue Transglutaminase (tTG) Antibody, IgA, Serum and IGA / Immunoglobulin A (IgA), Serum levels are recommended.

**Reference Values:**
Negative in normal individuals; also negative in dermatitis herpetiformis or celiac disease patients adhering to gluten-free diet.

**Clinical References:**

**English Plantain, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or ≥100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**Clinical References:** Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and Management by Laboratory Methods. 21st edition. Edited by RA McPherson, MR Pincus. WB Saunders
**Entamoeba histolytica Antibody, Serum**

**Clinical Information:** Amebiasis is an infection by the protozoan parasite, Entamoeba histolytica. The infection is acquired by ingestion of cysts in fecally contaminated food or water; excystation and infection occur in the large intestine. After excystation, trophozoites attach to the intestinal wall and liberate extracellular enzymes that enable invasion of the mucosa and spread to other organs, especially the liver and lung where abscesses develop. Amebiasis (or amebic dysentery) can cause bloody diarrhea accompanied by fever and prostration. Leukocytes, WBCs, and RBCs are found in the stools. Liver abscess can develop several weeks to months later producing hepatomegaly and fever. Pathogenic (E histolytica) and nonpathogenic (E dispar) species of Entamoeba occur. Additionally, some of those infected with pathogenic strains are asymptomatic cyst carriers.

**Useful For:** As an adjunct in the diagnosis of extraintestinal amebiasis, especially liver abscess

Serology may be particularly useful in supporting the diagnosis of amebic liver abscess in patients without a definite history of intestinal amebiasis and who have not spent substantial periods of time in endemic areas

**Interpretation:** A positive result suggests current or previous infection with Entamoeba histolytica. Since pathogenic and nonpathogenic species of Entamoeba cannot be differentiated microscopically, some authorities believe a positive serology indicates the presence of the pathogenic species (ie, E histolytica).

**Reference Values:**
Negative
Reference values apply to all ages.


**Entamoeba histolytica Antigen, EIA**

**Clinical Information:** Entamoeba histolytica are intestinal parasites that infect a half billion people worldwide annually. Of those infected, most are infected with the non-pathogenic E. dispar, which has not been associated with disease. It is estimated that approximately 10% of the half billion people infected each year are infected with the pathogenic E. histolytica. These individuals become symptomatic and develop colitis and liver abscesses. Limitations: Extraintestinal amebiasis is frequently found without trophozoites or cysts in stool: patients may have a negative stool antigen result.

**Reference Values:**
Entamoeba histolytica Antigen: Not Detected

The Entamoeba histolytica Antigen EIA test detects only the antigen of the pathogenic E. histolytica; the non-pathogenic E. dispar is not detected.

**Enteric Pathogens Culture, Stool**

**Clinical Information:** Diarrhea may be caused by a number of agents (eg, bacteria, viruses, parasites, and chemicals) and these agents may result in similar symptoms. A thorough patient history covering symptoms, severity, duration of illness, age, travel history, food consumption, history of recent antibiotic use, and illnesses in the family or other contacts will help the physician categorize the disease and ensure that any special requests are communicated to the laboratory.

**Useful For:** Determining whether a bacterial enteric pathogen is the cause of diarrhea May be helpful in identifying the source of the infectious agent (eg, dairy products, poultry, water, or meat)

**Interpretation:** The growth of an enteric pathogen identifies the cause of diarrhea.
Reference Values:
No growth of pathogens


Enterovirus, Molecular Detection, PCR

Clinical Information: Enteroviruses are positive-sense RNA viruses in the Picornaviridae family. These viruses were initially classified by serotype as polioviruses (3 types), echoviruses (31 types, including types 22 and 23, which are now classified as parechoviruses), coxsackievirus A (23 types), and coxsackievirus B (6 types). However, genomic studies have demonstrated that there is significant overlap in the biological characteristics of different serotypes and more recently isolated enteroviruses are now named with consecutive numbers (eg, EV68, EV69). The normal site of enterovirus replication is the gastrointestinal tract where the infection is typically subclinical. However, in a proportion of cases, the virus spreads to other organs, causing systemic manifestations, including mild respiratory disease (eg, the common cold); conjunctivitis; hand, foot, and mouth disease; aseptic meningitis; myocarditis; and acute flaccid paralysis. Collectively, enteroviruses are the most common cause of upper respiratory tract disease in children. In addition, the enteroviruses are the most common cause of central nervous system (CNS) disease; they account for almost all viruses recovered in culture from spinal fluid. Differentiation of enteroviruses from other viruses and bacteria that cause CNS disease is important for the appropriate medical management of these patients. Traditional cell culture methods require 6 days, on average, for enterovirus detection. In comparison, real-time PCR allows same-day detection. Detection of enterovirus nucleic acid by PCR is also the most sensitive diagnostic method for the diagnosis of CNS infection caused by these viruses.

Useful For: Aids in diagnosing enterovirus infections

Interpretation: A positive result indicates the presence of enterovirus RNA in the specimen.

Reference Values:
Negative

flaccid paralysis. Collectively, enteroviruses are the most common cause of upper respiratory tract disease in children. In addition, the enteroviruses are the most common cause of central nervous system (CNS) disease; they account for almost all viruses recovered in culture from spinal fluid. Differentiation of enteroviruses from other viruses and bacteria that cause CNS disease is important for the appropriate medical management of these patients. Traditional cell culture methods require 6 days, on average, for enterovirus detection. In comparison, real-time PCR allows same-day detection. Detection of enterovirus nucleic acid by PCR is also the most sensitive diagnostic method for the diagnosis of CNS infection caused by these viruses.

**Useful For:** Aids in diagnosing enterovirus infections

**Interpretation:** A positive result indicates the presence of enterovirus RNA in the specimen.

**Reference Values:**
Negative

**Clinical References:**

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**FECP**

**Eosinophil Cationic Protein (ECP)**

**Reference Values:**
2 â€“ 10 mcg/L

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**EOSU**

**Eosinophils, Urine**

**Clinical Information:** Eosinophils are white blood cells that normally do not appear in urine. The presence of eosinophils in the urine is seen in acute interstitial nephritis, which is caused by an allergic reaction, typically to drugs.

**Useful For:** Investigation of possible acute interstitial nephritis

**Interpretation:** Greater than 5% eosinophils indicates acute interstitial nephritis; 1% to 5% eosinophils is indeterminant.

**Reference Values:** None seen

**Clinical References:**
1. Hansel FK: In Clinical Allergy. CV Mosby Co. St. Louis, 1953

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**FEPHD**

**Ephedrine, Serum**

**Reference Values:**
Reference Range: 35 - 80 ng/mL

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**EPUR**

**Epicoccum purpurascens, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


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**Epidermal Nerve Fiber Density Consultation**

**Clinical Information:** Small fiber peripheral neuropathy is a common neurological complaint and a frequent source of morbidity in many patient populations. Direct investigation of small fiber involvement has been limited as most classical techniques such as electromyography (EMG), nerve conduction studies (NCS), and nerve biopsy, focus on large diameter nerve fibers and may be normal in patients with small fiber neuropathies. The advent of epidermal skin biopsies and PGP 9.5 immunohistochemistry allows the direct visualization and morphologic assessment of small sensory fibers innervating the skin.(1) Assessment of intraepidermal nerve fiber density has been used to reliably demonstrate pathologic abnormalities in small fiber neuropathy of various etiologies including diabetes, HIV, systemic lupus erythematosus, and neurosarcoïdosis. Further, the technique has been validated, shown to have acceptable sensitivity and specificity, and is minimally invasive. The publication of normative data for commonly tested sites such as the distal and proximal legs and arms permits direct comparison of patients to age- and sex-matched controls facilitating localization and diagnosis.(2-4) Based on class 1 evidence and American Medical Association CPT code review process acceptance, intraepidermal nerve fiber density (IENFD) measurements are now an accepted investigational method in the workup of polyneuropathy, including...
the characterization and diagnosis of varieties of length-dependent small fiber polyneuropathies. IEFND measurements have been incorporated in recent practice guidelines published by the American Academy of Neurology and the European Federation of Neurological Science.(5,6)

**Useful For:** Investigation of polyneuropathies

**Interpretation:** The number of intraepidermally originating nerve fibers that cross the basement membrane between the dermis and epidermis are counted in several sections.(2,5) The total linear length of the epidermis is measured using standard morphometric techniques and a density of epidermal nerve fibers (number of fibers/mm) is reported. This value is compared to previously published normative data.

**Reference Values:**
A consultative report will be provided.

**Clinical References:**

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**FEPI**

**Epidermophyton floccosum IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 ≤ 0.69 Low Positive 2 0.70 ≤ 3.49 Moderate Positive 3 3.50 ≤ 17.49 Positive 4 17.50 ≤ 49.99 Strong Positive 5 50.00 ≤ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

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**EPS1**

**Epilepsy, Autoimmune Evaluation, Serum**

**Clinical Information:** Antiepileptic drugs (AEDs) are the mainstay of treatment for epilepsy, but seizures continue in one-third of patients despite appropriate AED therapeutic trials. The etiology of epilepsy often remains unclear. Seizures are a common symptom in autoimmune neurological disorders, including limbic encephalitis and multifocal paraneoplastic disorders. Seizures may be the exclusive manifestation of an autoimmune encephalopathy without evidence of limbic encephalitis. Autoimmune epilepsy is increasingly recognized in the spectrum of neurological disorders characterized by detection of neural autoantibodies in serum or spinal fluid and responsiveness to immunotherapy. The advent of more sensitive and specific serological detection methods is increasingly revealing previously underappreciated autoimmune epilepsies. Neural autoantibodies specific for intracellular and plasma membrane antigens aid the diagnosis of autoimmune epilepsy, but no single antibody is specific for this diagnosis. Autoantibody specificities currently most informative for autoimmune epilepsies include voltage-gated potassium channel-complex (VGKC-complex), glutamic acid decarboxylase-65 (GAD65), N methyl-D-aspartate receptor (NMDAR),
alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR), and gamma aminobutyric acid type B receptor (GABABR) antibodies. Autoantibodies recognizing onconeural proteins shared by neurons, glia or muscle (eg, antineuronal nuclear antibody-type 1: ANNA 1, CRMP 5-IgG, N-type voltage-gated calcium channel and muscle AChR) also serve as markers of paraneoplastic or idiopathic autoimmune epilepsies. A specific neoplasm is often predictable by the individual patient's autoantibody profile. Suspicion for autoimmune epilepsy on clinical grounds justifies comprehensive evaluation of spinal fluid and serum for neural autoantibodies. Selective autoantibody testing is not advised because no single neural antibody is definitively associated with seizures, and markers of occult cancer may be missed. Failure to detect a neural antibody does not exclude the diagnosis of autoimmune epilepsy when other clinical clues exist. A trial of immunotherapy is justifiable in those cases.

**Useful For:** Investigating new onset cryptogenic epilepsy with incomplete seizure control and duration of less than 2 years Investigating new onset cryptogenic epilepsy plus 1 or more of the following accompaniments: -Psychiatric accompaniments (psychosis, hallucinations) -Movement disorder (myoclonus, tremor, dyskinesias) -Headache -Cognitive impairment/encephalopathy -Autoimmune stigmata (personal history or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, premature graying of hair, myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, idiopathic adrenocortical insufficiency), or multiple sclerosis -History of cancer -Smoking history (20+ pack years) or other cancer risk factors -Investigating seizures occurring within the context of a subacute multifocal neurological disorder without obvious cause, especially in a patient with past or family history of cancer -A rising autoantibody titer in a previously seropositive patient suggests cancer recurrence

**Interpretation:** Antibodies specific for neuronal, glial, or muscle proteins are valuable serological markers of autoimmune epilepsy and of a patient's immune response to cancer. These autoantibodies are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. It is not uncommon for more than 1 of the following autoantibodies to be detected in patients with autoimmune dementia. -Plasma membrane antibodies (N-methyl-D-aspartate: NMDA receptor; 2-amino-3-[5-methyl-3-oxo-1,2- oxazol-4-yl] propanoic acid: AMPA receptor; gamma-aminobutyric acid: GABA-B receptor). These autoantibodies are all potential effectors of dysfunction. -Neuronal nuclear autoantibody, type 1 (ANNA-1) or type 3 (ANNA-3). -Neuronal or muscle cytoplasmic antibodies (amphiphysin, Purkinje cell antibody-type 2: PCA-2, collapsin response-mediator protein-5 neuronal: CRMP-5-IgG, or glutamic acid decarboxylase: GAD65 antibody).

**Reference Values:**

**NEURONAL NUCLEAR ANTIBODIES**

Antineuronal Nuclear Ab, Type 1 (ANNA-1)  
<1:240

Antineuronal Nuclear Ab, Type 2 (ANNA-2)  
<1:240

Antineuronal Nuclear Ab, Type 3 (ANNA-3)  
<1:240

Anti-Glial/Neuronal Nuclear Ab, Type 1 (AGNA-1)  
<1:240

**NEURONAL AND MUSCLE CYTOPLASMIC ANTIBODIES**

Purkinje Cell Cytoplasmic Ab, Type 1 (PCA-1)  
<1:240

Purkinje Cell Cytoplasmic Ab, Type 2 (PCA-2)  
<1:240

Purkinje Cell Cytoplasmic Ab, Type Tr (PCA-Tr)  
<1:240

Amphiphysin Antibody  
<1:240

CRMP-5-IgG  
<1:240

**WESTERN BLOT**

Paraneoplastic Western Blot
Negative
CRMP-5-IgG Western Blot
Negative
Amphiphysin Western Blot
Negative

ISLET CELL ANTIBODIES
Glutamic Acid Decarboxylase (GAD65) Antibody
< or =0.02 nmol/L

CATION CHANNEL ANTIBODIES
N-Type Calcium Channel Antibody
< or =0.03 nmol/L
P/Q-Type Calcium Channel Antibody
< or =0.02 nmol/L
AChR Ganglionic Neuronal Antibody
< or =0.02 nmol/L
Neuronal VGKC Autoantibody
< or =0.02 nmol/L

ACHR RECEPTOR ANTIBODIES
ACh Receptor (Muscle) Binding Antibody
< or =0.02 nmol/L

N-Methyl-D-aspartate receptor (NMDA-R)
CBA: Negative
IFA: <1:120

2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid receptor (AMPA-R)
CBA: Negative
IFA: <1:120

Gamma-Amino Butyric acid-type B receptor (GABA-B-R)
CBA: Negative
IFA: <1:120
LGII-IgG CBA: Negative
CASP2R-IgG CBA: Negative

Neuromyelitis Optica (NMO)/Aquaporin-4-IgG FACS Assay, S
Negative


EPC1 48406

Epilepsy, Autoimmune Evaluation, Spinal Fluid

Clinical Information: Antiepileptic drugs (AEDs) are the mainstay of treatment for epilepsy, but seizures continue in one-third of patients despite appropriate AED therapeutic trials. The etiology of epilepsy often remains unclear. Seizures are a common symptom in autoimmune neurological disorders, including limbic encephalitis and multifocal paraneoplastic disorders. Seizures may be the exclusive manifestation of an autoimmune encephalopathy without evidence of limbic encephalitis. Autoimmune
epilepsy is increasingly recognized in the spectrum of neurological disorders characterized by detection of neural autoantibodies in serum or spinal fluid and responsiveness to immunotherapy. The advent of more sensitive and specific serological detection methods is increasingly revealing previously underappreciated autoimmune epilepsies. Neural autoantibodies specific for intracellular and plasma membrane antigens aid the diagnosis of autoimmune epilepsy, but no single antibody is specific for this diagnosis. Autoantibody specificities currently most informative for autoimmune epilepsies include voltage-gated potassium channel-complex (VGKC-complex), glutamic acid decarboxylase-65 (GAD65), N methyl-D-aspartate receptor (NMDAR), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR) and gamma aminobutyric acid type B receptor (GABABR) antibodies. Autoantibodies recognizing onconeuronal proteins shared by neurons, glia, or muscle (eg, antineuronal nuclear antibody, type 1: ANNA 1; collapsin response-mediator protein-5 neuronal: CRMP-5-IgG; N-type calcium channel antibody, and acetylcholine receptor [muscle AChR] binding antibody), also serve as markers of paraneoplastic or idiopathic autoimmune epilepsies. A specific neoplasm is often predictable by the individual patient's autoantibody profile. Suspicion for autoimmune epilepsy on clinical grounds justifies comprehensive evaluation of cerebral spinal fluid and serum for neural autoantibodies. Selective autoantibody testing is not advised because no single neural antibody is definitively associated with seizures, and markers of occult cancer may be missed. Failure to detect a neural antibody does not exclude the diagnosis of autoimmune epilepsy when other clinical clues exist. A trial of immunotherapy is justifiable in those cases.

Useful For: Investigating new onset cryptogenic epilepsy with incomplete seizure control and duration of less than 2 years Investigating new onset cryptogenic epilepsy plus 1 or more of the following accompaniments: -Psychiatric accompaniments (psychosis, hallucinations) -Movement disorder (myoclonus, tremor, dyskinesias) -Headache -Cognitive impairment/encephalopathy -Autoimmune stigmata (personal history or family history or signs of diabetes mellitus, thyroid disorder, vitiligo, premature graying of hair, myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, idiopathic adrenocortical insufficiency) or "multiple sclerosis" -History of cancer -Smoking history (20+ pack years) or other cancer risk factors -Investigating seizures occurring within the context of a subacute multifocal neurological disorder without -obvious cause, especially in a patient with past or family history of cancer

Interpretation: Antibodies specific for neuronal, glial, or muscle proteins are valuable serological markers of autoimmune epilepsy and of a patient's immune response to cancer. These autoantibodies are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. It is not uncommon for more than 1 of the following autoantibodies to be detected in patients with autoimmune epilepsy: -Plasma membrane antibodies (N-methyl-D-aspartate [NMDA] receptor; 2-amino-3-[5-methyl-3-oxo-1,2- oxazol-4-yl] propanoic acid [AMPA] receptor; gamma-amino butyric acid [GABA-B] receptor). These autoantibodies are all potential effectors of dysfunction. -Neuronal nuclear autoantibody, type 1 (ANNA-1) or type 3 (ANNA-3). -Neuronal or muscle cytoplasmic antibodies (amphiphysin, Purkinje cell antibody-type 2 [PCA-2], collapsin response-mediator protein-5 neuronal [CRMP-5-IgG], or glutamic acid decarboxylase [GAD65] antibody). A rising autoantibody titer in a previously seropositive patient suggests cancer recurrence.

Reference Values:

NEURONAL NUCLEAR ANTIBODIES
Antineuronal Nuclear Antibody-Type 1 (ANNA-1) <1:2
Antineuronal Nuclear Antibody-Type 2 (ANNA-2) <1:2
Antineuronal Nuclear Antibody-Type 3 (ANNA-3) <1:2
Anti-Glial/Neuronal Nuclear Antibody-Type 1 (AGNA-1) <1:2

NEURONAL AND MUSCLE CYTOPLASMIC ANTIBODIES
Purkinje Cell Cytoplasmic Antibody, Type 1 (PCA-1) <1:2
Purkinje Cell Cytoplasmic Antibody, Type 2 (PCA-2)
Purkinje Cell Cytoplasmic Antibody, Type TR (PCA-TR)
<1:2
Amphiphysin Antibody
<1:2
Collapsin Response-Mediator Protein-5 Neuronal (CRMP-5-IGG)
<1:2

ISLET CELL ANTIBODIES
Glutamic Acid Decarboxylase (GAD65) Antibody Assay
< or =0.02 nmol/L

AMPA-Receptor Antibody By CBA
CBA: Negative
IFA: <1:2
GABA-B-Receptor Antibody By CBA
CBA: Negative
IFA: <1:2
NMDA-Receptor Antibody By CBA
CBA: Negative
IFA: <1:2

Neuronal Voltage-Gated Potassium Channel-Complex Autoantibody
< or =0.02 nmol/L

WESTERN BLOT
Paraneoplastic Autoantibody, Western Blot Confirmation
Negative
Collapsin Response-Mediator Protein-5-IGG (CRMP-5-IGG) Western Blot
Negative
Amphiphysin Antibody Western Blot
Negative
LGI1-IgG CBA: Negative
CASPR2-IgG CBA: Negative

Neuromyelitis Optica (NMO)/Aquaporin-4-Igg FACS Assay
Negative

sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


**Epithelia Panel # 2**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the
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### Epithelial Membrane Antigen (EMA) Immunostain, Technical Component Only

**Clinical Information:** Epithelial membrane antigen (EMA) is expressed by epithelial cells of all types, mesothelial cells, perineural cells, and a subset of plasma cells. EMA is expressed by meningiomas, synovial sarcoma, epithelioid sarcoma, a subset of peripheral nerve sheath tumors, the lymphocyte-predominant cells of lymphocyte-predominant Hodgkin lymphoma, and anaplastic large cell lymphoma. Diagnostically, EMA is useful in recognizing epithelial derivation of poorly differentiated malignant tumors.

**Useful For:** Aids in recognizing epithelial derivation of poorly differentiated malignant tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
**EBNA2**

**Epstein Barr Nuclear Antigen 2 (EBNA2) Immunostain, Technical Component Only**

**Clinical Information:** Epstein Barr virus (EBV) nuclear antigen 2 (EBNA2) is an EBV-encoded nuclear protein of 82 kD. EBNA2 is necessary for transformation of EBV-infected B lymphocytes and has been shown to modulate the activity of several viral and cellular promoters. This immunostain may be useful in the diagnosis of reactive and neoplastic lymphoproliferative and plasma cell proliferative disorders.

**Useful For:** Aids in the identification of Epstein Barr virus infection in normal, inflammatory, and neoplastic tissues

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**LMP1**

**Epstein Barr Virus Latency Membrane Protein 1 (EBV-LMP1) Immunostain, Technical Component Only**

**Clinical Information:** The latent membrane protein 1 (LMP-1) oncogene of Epstein-Barr virus (EBV) is believed to contribute to the development of many EBV-associated tumors. This antibody may be useful in the diagnosis of reactive and neoplastic lymphoproliferative and plasma cell proliferative disorders.

**Useful For:** Aids in the identification of Epstein Barr virus infection in normal, inflammatory, and neoplastic tissues

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
Epstein-Barr Virus (EBV) Antibody Profile, Serum

Clinical Information: Epstein-Barr virus (EBV), a member of the herpesvirus group, is the etiologic agent of infectious mononucleosis. EBV infections are difficult to diagnose in the laboratory since the virus does not grow in standard cell cultures. The majority of infections can be recognized, however, by testing the patient's serum for heterophile antibodies (rapid latex slide agglutination test; eg, MONOS / Infectious Mononucleosis, Rapid Test, Serum), which usually appear within the first 3 weeks of illness, but then decline rapidly within a few weeks. The heterophile antibody, however, fails to develop in about 10% of adults, more frequently in children, and almost uniformly in infants with primary EBV infections. Most of these heterophile antibody-negative cases of infectious mononucleosis-like infections are due to cytomegalovirus, but in a series of 43 cases, EBV was the cause in 7. In cases where EBV is suspected, but the heterophile antibody is not detected, an evaluation of the EBV-specific antibody profile (eg, EBV viral capsid antigen: VCA IgM, EBV VCA IgG, and EBV nuclear antigen: EBNA) may be useful. Infection with EBV usually occurs early in life. For several weeks to months after acute onset of the infection, it is spread by upper respiratory secretions that contain the virus. Among the clinical disorders due to EBV infection, infectious mononucleosis is the most common. Other disorders due to EBV infection have been recognized for several years, including African-type Burkitt lymphoma and nasopharyngeal carcinoma. EBV infection may also cause lymphoproliferative syndromes, especially in patients who have undergone renal or bone marrow transplantation and in those who have AIDS.

Useful For: Diagnosing infectious mononucleosis when a mononucleosis screening procedure is negative and infectious mononucleosis or a complication of Epstein-Barr virus infection is suspected

Interpretation: The test has 3 components: viral capsid antigen (VCA) IgG, VCA IgM, and Epstein-Barr nuclear antigen (EBNA). Presence of VCA IgM antibodies indicates recent primary infection with Epstein-Barr virus (EBV). The presence of VCA IgG antibodies indicates infection sometime in the past. Antibodies to EBNA develop 6 to 8 weeks after primary infection and are detectable for life. Over 90% of the normal adult population has IgG class antibodies to VCA and EBNA. Few patients who have been infected with EBV will fail to develop antibodies to the EBNA (approximately 5%-10%). Possible Results VCA IgG VCA IgM EBNA IgG Interpretation - - - No previous exposure + + - Recent infection + - + Past infection + - - See note* + + + Past infection *Results indicate infection with EBV at some time (VCA IgG positive). However, the time of the infection cannot be predicted (ie, recent or past) since antibodies to EBNA usually develop after primary infection (recent) or, alternatively, approximately 5% to 10% of patients with EBV never develop antibodies to EBNA (past).

Reference Values:
Epstein-Barr Virus (EBV) VIRAL CAPSID ANTIGEN (VCA) IgM ANTIBODY Negative

Epstein-Barr Virus (EBV) VIRAL CAPSID ANTIGEN (VCA) IgG ANTIBODY Negative

EPSTEIN-BARR NUCLEAR ANTIGEN (EBNA) ANTIBODIES Negative

Epstein-Barr Virus (EBV) In Situ Hybridization, Technical Component Only

Clinical Information: Epstein-Barr virus (EBV) plays a pathogenic role in a variety of disease states, including infectious mononucleosis, nasopharyngeal carcinoma, Burkitt lymphoma, B-cell lymphomas in patients with congenital or acquired immunodeficiency, and some cases of classical Hodgkin lymphoma.

Useful For: Detection of Epstein-Barr virus (EBV)-encoded RNA (EBER) in the diagnosis of EBV-associated conditions

Interpretation: The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Epstein-Barr Virus (EBV), IgG Antibody to Early Antigen, Serum

Clinical Information: Epstein-Barr virus (EBV), a member of the herpesvirus group, is the etiologic agent of infectious mononucleosis. EBV infections are difficult to diagnose in the laboratory since the virus does not grow in standard cell cultures. The majority of infections can be recognized, however, by testing the patient's serum for heterophile antibodies (rapid latex slide agglutination test; eg, MONOS / Infectious Mononucleosis Rapid Test, Serum). Heterophile antibodies usually appear within the first 3 weeks of illness, but then decline rapidly within a few weeks. The heterophile antibody, however, fails to develop in about 10% of adults, more frequently in children, and almost uniformly in infants with primary EBV infections. Most of these heterophile antibody negative cases of infectious mononucleosis-like infections are due to cytomegalovirus, but in 1 series of 43 cases, EBV was the cause in 7. In cases where EBV is suspected but the heterophile antibody is not detected, an evaluation of EBV-specific antibodies (eg, IgM and IgG antibodies to EBV viral capsid antigen: VCA) and antibodies to EBV nuclear antigen (EBNA) may be useful. The EBV EIA tests that detect antibodies to the EBV VCA and early antigen (EA) are more sensitive than heterophile antibody tests. Infection with EBV usually occurs early in life. For several weeks to months after acute onset of the infection, it is spread by upper respiratory secretions that contain the virus. Among the clinical disorders due to EBV infection, infectious mononucleosis is the most common. Other disorders due to EBV infection include African-type Burkitt lymphoma and nasopharyngeal carcinoma (NPC). EBV infection may also cause lymphoproliferative syndromes, especially in patients with AIDS and in patients who have undergone renal or bone marrow transplantation. Using immunofluorescent staining techniques, 2 patterns of EA are seen, 1) diffuse staining of both cytoplasm and nucleus (early antigen-diffuse; EA-D) and 2) cytoplasmic or early antigen restricted (EA-R). Antibodies responsible for the diffuse staining pattern (EA-D) are seen in infectious mononucleosis and NPC, and are measured in this assay.

Useful For: A third-order test in the diagnosis of infectious mononucleosis, especially in situations when initial testing results (heterophile antibody test) are negative and follow-up testing (viral capsid antigen: VCA IgG, VCA IgM, and Epstein-Barr nuclear antigen) yields inconclusive results aiding in the diagnosis of type 2 or type 3 nasopharyngeal carcinoma

Interpretation: The presence of antibody to the early antigen (EA) of Epstein-Barr virus (EBV)
indicates that EBV is actively replicating. Generally, this antibody can only be detected during active EBV infection, such as in patients with infectious mononucleosis. Clinical studies have indicated that patients who have chronic active or reactivated EBV infection commonly have elevated levels of IgG-class antibodies to the EA of EBV. IgG antibody specific for the diffuse early antigen of EBV is often found in patients with nasopharyngeal carcinoma (NPC). Of patients with type 2 or 3 NPC (World Health Organization classification), 94% and 83% respectively, have positive-antibody responses to EA. Only 35% of patients with type 1 NPC have a positive response. The specificity of the test is such that 82% to 91% of healthy blood donor controls and patients who do not have NPC have negative responses (9%-18% false-positives). Although this level of specificity is useful for diagnostic purposes, the false-positive rate indicates that the test is not useful for NPC screening.

**Reference Values:**
Negative
Reference values apply to all ages.


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**Epstein-Barr Virus (EBV), Molecular Detection, PCR**

**Clinical Information:** Epstein-Barr virus (EBV) is the causative agent of infectious mononucleosis, Burkitt lymphoma, and in Southern China, nasopharyngeal carcinoma. EBV-associated central nervous system (CNS) disease is most commonly associated with primary CNS lymphoma in patients with AIDS. In addition, CNS infection associated with the detection of EBV DNA can be seen in immunocompetent patients.

**Useful For:** Rapid qualitative detection of Epstein-Barr virus (EBV) DNA in specimens for laboratory diagnosis of disease due to this virus

**Interpretation:** Detection of Epstein-Barr virus (EBV) DNA in cerebrospinal fluid (CSF) supports the clinical diagnosis of central nervous system (CNS) disease due to the virus. EBV DNA is not detected in CSF from patients without CNS disease caused by this virus.

**Reference Values:**
Negative


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**Epstein-Barr Virus DNA Detection and Quantification, Plasma**

**Clinical Information:** Primary infection with Epstein-Barr virus (EBV), a DNA virus in the Herpesviridae family, may cause infectious mononucleosis resulting in a benign lymphoproliferative...
condition characterized by fever, fatigue, sore throat, and lymphadenopathy. Infection occurs early in life, and by 10 years of age, 70% to 90% of children have been infected with this virus. Usually, infection in children is asymptomatic or mild and may be associated with minor illnesses such as upper respiratory tract infection, pharyngitis, tonsillitis, bronchitis, and otitis media. The target cell for EBV infection is the B-lymphocyte. Immunocompromised individuals lacking antibody to EBV are at risk for acute EBV infection that may cause lymphoproliferative disorders in organ transplant recipients (posttransplant lymphoproliferative disorders [PTLD]) and AIDS-related lymphoma. The incidence of PTLD ranges from 1% for renal transplant recipients to as high as 9% for heart/lung transplants and 12% for pancreas transplant patients. EBV DNA can be detected in the blood of patients with this viral infection, and increasing serial levels of EBV DNA in plasma have been shown to correlate highly with subsequent (in 3-4 months) development of PTLD in susceptible patients. Organ transplant recipients who are sero-negative (at risk for primary EBV infection) for EBV (most often children) who receive antilymphocyte globulin for induction immunosuppression and OKT-3 treatment for early organ rejection are at highest risk for developing PTLD when compared to immunologically normal individuals with prior EBV infection.

Useful For:
- Diagnosis of EBV-associated infectious mononucleosis in individuals with equivocal or discordant Epstein-Barr virus (EBV) serologic marker test results
- Diagnosis of posttransplant lymphoproliferative disorders (PTLD), especially in EBV-seronegative organ transplant recipients receiving antilymphocyte globulin for induction immunosuppression and OKT-3 treatment for early organ rejection
- Monitoring progression of EBV-associated PTLD in organ transplant recipients

Interpretation:
The quantification range of this assay is 100 to 5,000,000 IU/mL (or 2.00-6.70 log IU/mL), with a limit of detection (based on a 95% detection rate) at 45 IU/mL (1.65 log IU/mL). Increasing levels of Epstein-Barr virus (EBV) DNA in serial plasma specimens of a given organ transplant recipient may indicate possible development of posttransplant lymphoproliferative disorder (PTLD). An "Undetected" result indicates that EBV DNA is not detected in the plasma specimen (see Cautions). If clinically indicated, repeat testing in 1 to 2 months is recommended. A result of "<100 IU/mL" indicates that the EBV DNA level present in the plasma specimen is below 100 IU/mL (or 2.00 log IU/mL), and the assay cannot accurately quantify the EBV DNA present below this level. A quantitative value (reported in IU/mL and log IU/mL) indicates the EBV DNA level (ie, viral load) present in the plasma specimen. A result of ">5,000,000 IU/mL" indicates that the EBV DNA level present in the plasma specimen is above 5,000,000 IU/mL (6.70 log IU/mL), and this assay cannot accurately quantify the EBV DNA present above this level. An "Inconclusive" result indicates that the presence or absence of EBV DNA in the plasma specimen could not be determined with certainty after repeat testing in the laboratory, possibly due to PCR inhibition or presence of interfering substance. Submission of a new specimen for testing is recommended if clinically indicated.

Reference Values:
Undetected

Clinical References:

Clinical Information: The mammalian excision repair cross complementing (ERCC1) polypeptide is required for nucleotide excision repair (NER) of damaged DNA. The NER mechanism involves dual incisions on both sides of the damage catalyzed by 2 nucleases. In mammalian cells, XPG cleaves 3’ of the DNA lesion, while the ERCC1-XPF complex makes the 5’ incision. Elevated levels of the ERCC1 protein have been associated with increased risk of cancer. However, the clinical implications of this finding are not yet fully understood.

ERCC-1 Immunostain, Technical Component Only
Clinical Information: The mammalian excision repair cross complementing (ERCC1) polypeptide is required for nucleotide excision repair (NER) of damaged DNA. The NER mechanism involves dual incisions on both sides of the damage catalyzed by 2 nucleases. In mammalian cells, XPG cleaves 3’ of the DNA lesion, while the ERCC1-XPF complex makes the 5’ incision. Elevated levels of the ERCC1 protein have been associated with increased risk of cancer. However, the clinical implications of this finding are not yet fully understood.
have also been reported in Cisplatin-resistant cells.

**Useful For:** Determining excision repair cross complementing (ERCC1) polypeptide levels in cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**ERG Immunostain, Technical Component Only**

**Clinical Information:** ETS-related gene (ERG) is a member of the erythroblast transformation specific (ETS) family of transcription factors. Expression of ERG is observed in prostate cancers where the TMPRSS2-ERG gene rearrangement has occurred.

**Useful For:** Identification of ERG protein expression

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**Erythrocytosis Evaluation**

**Clinical Information:** Erythrocytosis (polycythemia) is identified by a sustained increase in hemoglobin or hematocrit. An isolated increase in RBC count (in the absence of chronic phlebotomy or coincident iron deficiency) is not within the definition of erythrocytosis and may occur in thalassemia or other causes. Erythrocytosis may occur as a primary disorder, due to an intrinsic defect of bone marrow stem cells, or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary
erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide, cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other EPO-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be present. It is important to differentiate polycythemia vera (PV) from heritable causes of erythrocytosis, the latter of which can be passed to progeny but do not carry the risks of clonal evolution associated with PV. The most common cause of hereditary erythrocytosis is the presence of a high-oxygen-affinity hemoglobin (HOA). A subset of hemoglobins with increased oxygen (O2) affinity result in clinically evident erythrocytosis caused by decreased O2 unloading at the tissue level. The most common symptoms are headache, dizziness, tinnitus, and memory loss. The affected individuals are plethoric, but not cyanotic. Patients with a HOA hemoglobin may present with an increased hemoglobin concentration, and hematocrit, but normal leukocyte and platelet counts. The p50 values are low. Changes to the amino acid sequence of the hemoglobin molecule may distort the molecular structure, affecting O2 transport and the binding of 2,3-BPG. 2,3-BPG is critical to O2 transport of erythrocytes because it regulates the O2 affinity of hemoglobin. A decrease in the 2,3-BPG concentration within erythrocytes results in greater O2 affinity of hemoglobin and reduction in O2 delivery to tissues. A few cases of erythrocytosis have been described as being due to a reduction in 2,3-BPG formation. This is most commonly due to mutations in the converting enzyme, bisphosphoglycerate mutase (BPGM). Mutations in the genes EPOR, EPAS1 (HIF2A), EGLN1 (PHD2), and VHL also cause hereditary erythrocytosis and a subset are associated with pheochromocytoma and paragangliomas. The prevalence of these mutations is unknown, but they appear less prevalent than mutations that cause high-oxygen-affinity hemoglobin variants, and much less prevalent than polycythemia vera. Because there are many causes of erythrocytosis, an algorithmic and reflexive testing strategy is useful. Initial JAK2 V617F mutation testing and serum EPO levels are important with p50 results further stratifying JAK2-negative cases. A significant subset of HOA hemoglobin variants can be electrophoretically silent; however, most if not all of these can be isolated with addition of the mass spectrometry method. Our extensive experience with these disorders allows an economical, comprehensive evaluation with high sensitivity.

Useful For: Definitive, comprehensive, and economical evaluation of an individual with JAK2-negative erythrocytosis associated with lifelong sustained increased hemoglobin or hematocrit

Interpretation: The evaluation includes testing for a hemoglobinopathy and oxygen (O2) affinity of the hemoglobin molecule. An increase in O2 affinity is demonstrated by a shift to the left in the O2 dissociation curve (decreased p50 result). Reflex testing for EPOR, EGLN1 (PHD2), EPAS1 (HIF2a), VHL, and BPGM will be performed as needed. A hematopathologist expert in these disorders will evaluate the case, appropriate tests are performed, and an interpretive report is issued.

Reference Values: Definitive results and an interpretive report will be provided.


Erythropoietin (EPO), Serum

Clinical Information: Erythropoietin (EPO), a large (193 amino acid residue) glycoprotein hormone secreted by the kidney, regulates RBC production. Normally, EPO levels vary inversely with hematocrit. Hypoxia stimulates EPO release, which, in turn, stimulates bone marrow erythrocyte production. High blood levels of RBC, hemoglobin, hematocrit, or oxygen suppress the release of EPO. Primary
polycythemia (polycythemia vera) is a neoplastic (clonal) blood disorder characterized by autonomous production of hematopoietic cells. Increased erythrocytes result in compensatory suppression of EPO levels. Findings consistent with polycythemia vera include hemoglobin >18.5 gm/dL, persistent leukocytosis, persistent thrombocytosis, unusual thrombosis, splenomegaly, and erythromelalgia (dysesthesia and erythema involving the distal extremities). Secondary polycythemias may either be due to an appropriate or an inappropriate increase in red cell mass. Appropriate secondary polycythemias (eg, high-altitude living and pulmonary disease) are characterized by hypoxia and a compensatory increase in red cell mass. EPO production is increased in an attempt to increase the delivery of oxygen by increasing the number of oxygen-carrying RBCs. Some tumors secrete EPO or EPO-like proteins; examples include tumors of the kidney, liver, lung, and brain. Such increases result in inappropriate secondary polycythemias. Abnormal EPO levels also may be seen in renal failure. The majority of EPO production is in the kidneys. Therefore, chronic renal failure may result in decreased renal EPO production and, subsequently, anemia. In addition to the kidneys, the liver also produces a small amount of EPO. Thus, anephric patients have a residual amount of EPO produced by the liver. Chronic renal failure patients, as well as patients with anemia due to a variety of other causes including chemotherapy, HIV/AIDS, and some hematologic disorders may be candidates for treatment with recombinant human EPO. Recombinant EPO compounds used to treat anemia include epoetin alpha and darbepoetin. Epoetin alpha is a 165 amino acid glycoprotein produced in mammalian cells and has an identical amino acid sequence to natural human EPO. It has 3 oligosaccharide chains and a molecular mass of 30.4 kDa. Darbepoetin alpha is a 165 amino acid glycoprotein that is also produced in mammalian cells. It has 2 additional N-linked oligosaccharide chains and a molecular mass of 37 kDa. There are no specific assays for measuring recombinant EPO compounds. Drug levels can only be roughly estimated from the cross reactivity of the compounds in EPO assays. According to in-house studies, epoetin and darbepoetin show approximately 58% and 36% cross-reactivity, respectively, in the EPO assay.

**Useful For:**
An aid in distinguishing between primary and secondary polycythemia Differentiating between appropriate secondary polycythemia (eg, high-altitude living, pulmonary disease, tobacco use) and inappropriate secondary polycythemia (eg, tumors) Identifying candidates for erythropoietin (EPO) replacement therapy (eg, chronic renal failure) Evaluating patients undergoing EPO replacement therapy who demonstrate an inadequate hematopoietic response

**Interpretation:**
In the appropriate clinical setting (eg, confirmed elevation of hemoglobin >18.5 gm/dL, persistent leukocytosis, persistent thrombocytosis, unusual thrombosis, splenomegaly, and erythromelalgia), polycythemia vera is unlikely when erythropoietin (EPO) levels are elevated and polycythemia vera is likely when EPO levels are suppressed. EPO levels are also increased in patients with anemia of bone marrow failure, iron deficiency, or thalassemia. Patients, who have either a poor or no erythropoietic response to EPO therapy, but high-normal or high EPO levels, may have additional, unrecognized cause(s) for their anemia. If no contributing factors can be identified after adequate further study, the possibility that the patient may have developed EPO-antibodies should be considered.

This can be a serious clinical situation that can result in red cell aplasia, and should prompt expeditious referral to hematologists or immunologists skilled in diagnosing and treating this disorder.

**Reference Values:**
2.6-18.5 mIU/mL

**Clinical References:**
number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other EPO-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be suspected. Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases is associated with pheochromocytoma and/or paraganglioma formation. It is caused by mutations in several genes and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these cases, although it is possible for new mutations to arise in an individual. The genes coding for hemoglobin, beta globin and alpha globin (high-oxygen-affinity hemoglobin variants), hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase: BPGM), and the erythropoietin receptor, EPOR, and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF/EPAS1, prolyl hydroxylase domain: PHD2/EGLN1, and von Hippel Lindau: VHL) can result in hereditary erythrocytosis (see Table). High-oxygen-affinity hemoglobin variants and BPGM abnormalities result in a decreased p50 result, whereas those affecting EPOR, HIF, PHD, and VHL have normal p50 results. The true prevalence of hereditary erythrocytosis-causing mutations is unknown. Genes Associated with Hereditary Erythrocytosis Gene Inheritance Serum EPO p50 JAK2 V617F Acquired Decreased Normal JAK2 exon 12 Acquired Decreased Normal EPOR Dominant Decreased to normal level Normal PHD2/EGLN1 Dominant Normal level Normal BPGM Recessive Normal level Decreased Beta Globin Dominant Normal level to increased Decreased Alpha Globin Dominant Normal level to increased Decreased HIF2A/EPAS1 Dominant Normal level to increased Normal VHL Recessive Markedly Increased Normal The oxygen-sensing pathway functions through an enzyme, hypoxia-inducible factor (HIF), which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including EPO, VEGF, and GLUT1. HIF-alpha is regulated by von Hippel-Lindau (VHL) protein-mediated ubiquitination and proteosomal degradation, which requires prolyl hydroxylation of HIF proline residues. The HIF-alpha subunit is encoded by the HIF2A (official name EPAS1) gene. Enzymes important in the hydroxylation of HIF-alpha are the prolyl hydroxylase domain proteins, of which the most significant isoform is PHD2, which is encoded by the PHD2 (official name EGLN1) gene. Mutations resulting in altered HIF-alpha, PHD2, and VHL proteins can lead to clinical erythrocytosis. A small subset of mutations, in PHD2 and HIF2A, has also been detected in erythrocytic patients presenting with paragangliomas or pheochromocytomas. Truncating mutations in the EPOR gene coding for the erythropoietin receptor can result in erythrocytosis through loss of the negative regulatory cytoplasmic SHP-1 binding domain leading to EPO hypersensitivity. All currently known mutations have been localized to exon 8, are mainly missense or small deletion and insertions resulting in stop codons, and are heterozygous. EPOR mutations are associated with decreased to normal EPO levels and normal p50 values (see Table).

**Useful For:** The definitive evaluation of an individual with JAK2-negative erythrocytosis associated with lifelong sustained increased RBC mass, elevated RBC count, hemoglobin, or hematocrit

**Interpretation:** An interpretive report will be provided as a part of the HEMP / Hereditary Erythrocytosis Mutations, and will include specimen information, assay information, and whether the specimen was positive for any mutations in the gene. If positive, the mutation will be correlated with clinical significance, if known.

**Reference Values:**
Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations.

An interpretive report is provided.

**Clinical References:**
### Estradiol Free, Serum (includes Estradiol and SHBG)

#### Reference Values:

**Estradiol, Serum MS**  
**Units:** pg/mL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>Levels are markedly elevated at birth and fall rapidly during the first week to prepubertal values of &lt;15.</td>
</tr>
<tr>
<td>Males &lt;6 m</td>
<td>Levels increase to 10 - 32 between 30 and 60 days, then decline to prepubertal levels of &lt;15 by six months.</td>
</tr>
<tr>
<td>Females &lt;1 y</td>
<td>Levels increase to 5.0 - 50 between 30 and 60 days, then decline to prepubertal levels of &lt;15 during the first year.</td>
</tr>
<tr>
<td>Prepubertal</td>
<td>&lt;15</td>
</tr>
<tr>
<td>Adult Males</td>
<td>8.0 - 35</td>
</tr>
<tr>
<td>Adult Females</td>
<td></td>
</tr>
<tr>
<td>Follicular</td>
<td>30 - 100</td>
</tr>
<tr>
<td>Luteal</td>
<td>70 - 300</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

**Free Estradiol, Percent**  
**Units:** %

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Males</td>
<td>1.7 - 5.4</td>
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<tr>
<td>Adult Females</td>
<td>1.6 - 3.6</td>
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</tbody>
</table>

**Free Estradiol, Serum**  
**Units:** pg/mL

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Males</td>
<td>0.2 - 1.5</td>
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<tr>
<td>Adult Females</td>
<td>0.6 - 7.1</td>
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</tbody>
</table>

**Sex Hormone Binding Globulin**  
**Units:** nmol/L

<table>
<thead>
<tr>
<th>Age</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants (1 - 23m)</td>
<td>60.0 - 252.0</td>
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<tr>
<td>Prepubertal</td>
<td>72.0 - 220.0</td>
</tr>
<tr>
<td>Pubertal Males</td>
<td>16.0 - 100.0</td>
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<tr>
<td>Pubertal Females</td>
<td>36.0 - 125.0</td>
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<tr>
<td>Adult Males</td>
<td>16.5 - 55.9</td>
</tr>
<tr>
<td>Adult Females</td>
<td>19.3 - 76.4</td>
</tr>
<tr>
<td>Adult Females</td>
<td>24.6 - 122.0</td>
</tr>
<tr>
<td>Adult Females</td>
<td>17.3 - 125.0</td>
</tr>
</tbody>
</table>

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  Page 831
Estradiol, Rapid, Immunoassay, Serum

Clinical Information: Estrogens are responsible for the development and maintenance of female sex organs and female secondary sex characteristics. In conjunction with progesterone, they participate in regulation of the menstrual cycle, breast and uterine growth, and in the maintenance of pregnancy. Estrogens affect calcium homeostasis and have a beneficial effect on bone mass. They decrease bone resorption and, in prepubertal girls, estrogen accelerates linear bone growth. Long-term estrogen depletion is associated with loss of bone mineral content, an increase in stress fractures, and postmenopausal osteoporosis. The 3 most biologically active estrogens in order of potency are estrone (E1), estradiol (E2), and estriol (E3). Estrogens are produced primarily in the ovary (follicle, corpus luteum), but small quantities are also formed in the testes and in the adrenal cortex. During pregnancy, estrogens are mainly formed in the placenta. About 98% of estradiol is bound to transport proteins (sex hormone-binding globulin: SHBG) and albumin. Estrogen secretion is biphasic during the menstrual cycle. The determination of estradiol is utilized clinically in the elucidation of fertility disorders in the hypothalamus-pituitary-gonad axis, gynecomastia, estrogen-producing ovarian and testicular tumors, and in hyperplasia of the adrenal cortex. Additional clinical indications are the monitoring of fertility therapy and determining the time of ovulation within the framework of in vitro fertilization (IVF). The laboratory plays an important role in the process of ovulation induction. The principle involves administration of gonadotropins to stimulate follicular growth, followed by human chorionic gonadotropin (hCG) to stimulate ovulation follicular maturation. Clinical, laboratory, and ultrasound monitoring of the treatment cycle is necessary to identify the dose and length of therapy, determine when or whether to administer hCG, and obtain an adequate ovulatory response while avoiding hyperstimulation. For other clinical indications, order EEST / Estradiol, Serum.

Useful For: Rapid assessment of ovarian status, including follicle development, for assisted reproduction protocols (eg, in vitro fertilization) Establishing time of ovulation and optimal time for conception

Interpretation: Optimal time for conception is within 48 to 72 hours following the midcycle estradiol peak. Serial specimens must be drawn over several days to evaluate baseline and peak estradiol levels. Low baseline levels and a lack of rise, as well as persistent high levels without midcycle rise, are indicative of anovulatory cycles. For determining the timing of initiation of ovarian stimulation in in vitro fertilization (IVF) studies, low levels before stimulation are critical, as higher values often are associated with poor stimulation cycles. Before final human chorionic gonadotropin (hCG) stimulation at mid-IVF cycle, estradiol concentrations above 2,000 to 3,000 pg/mL are considered by some IVF specialists to be indicative of an increased likelihood of ovarian hyperstimulation and it may be advisable to consider withholding further hCG stimulation. Estradiol (E2) concentrations below 200 pg/mL following midcycle stimulation (hCG or follicle-stimulating hormone: FSH) are associated with very low pregnancy success rates. E2 concentrations change during the menstrual cycle, as follows: -less than 50 pg/mL before midfollicular phase -250 to 500 pg/mL midcycle peak as the follicle matures -Abrupt decrease after ovulation -125 pg/mL peak during the luteal phase Estrogen replacement in reproductive-age women should aim to mimic natural estrogen levels as closely as possible. E2 levels should be within the reference range for premenopausal women and luteinizing hormone (LH) and follicle-stimulating hormone (FSH) should be within the normal range.

Reference Values:
Males: 10-40 pg/mL
Females
  Premenopausal: 15-350 pg/mL*
  Postmenopausal: <10 pg/mL
*Estradiol concentrations vary widely throughout the menstrual cycle
The limit of quantitation for estradiol measured by immunoassay is 25 pg/mL. Mass spectrometry is the preferred method for measurement of low serum estradiol concentrations in children, males and postmenopausal females (EEST / Estradiol, Serum).

Clinical Information:

Estrogens are involved in development and maintenance of the female phenotype, germ cell maturation, and pregnancy. They also are important for many other, nongender-specific processes, including growth, nervous system maturation, bone metabolism/remodeling, and endothelial responsiveness. The 2 major biologically active estrogens in nonpregnant humans are estrone (E1) and estradiol (E2). A third bioactive estrogen, estril (E3), is the main pregnancy estrogen, but plays no significant role in nonpregnant women or men. E2 is produced primarily in ovaries and testes by aromatization of testosterone. Small amounts are produced in the adrenal glands and some peripheral tissues, most notably fat. By contrast, most of the circulating E1 is derived from peripheral aromatization of androstenedione (mainly adrenal). E2 and E1 can be converted into each other, and both can be inactivated via hydroxylation and conjugation. E2 demonstrates 1.25 to 5 times the biological potency of E1. E2 circulates at 1.5 to 4 times the concentration of E1 in premenopausal, nonpregnant women. E2 levels in men and postmenopausal women are much lower than in nonpregnant women, while E1 levels differ less, resulting in a reversal of the premenopausal E2:E1 ratio. E2 levels in premenopausal women fluctuate during the menstrual cycle. They are lowest during the early follicular phase. E2 levels then rise gradually until 2 to 3 days before ovulation, at which stage they start to increase much more rapidly and peak just before the ovulation-inducing luteinizing hormone (LH)/follicle stimulating hormone (FSH) surge at 5 to 10 times the early follicular levels. This is followed by a modest decline during the ovulatory phase. E2 levels then increase again gradually until the midpoint of the luteal phase and, thereafter, decline to trough, early follicular levels.

Measurement of serum E2 forms an integral part of the assessment of reproductive function in females, including assessment of infertility, oligo-amenorrhea, and menopausal status. In addition, it is widely used for monitoring ovulation induction, as well as during preparation for in vitro fertilization. For these applications E2 measurements with modestly sensitive assays suffice. However, extra sensitive E2 assays, simultaneous measurement of E1, or both are needed in a number of other clinical situations. These include inborn errors of sex steroid metabolism, disorders of puberty, estrogen deficiency in men, fracture risk assessment in menopausal women, and increasingly, therapeutic drug monitoring, either in the context of low-dose female hormone replacement therapy or antiestrogen treatment. See Steroid Pathways in Special Instructions.

Useful For:

All applications that require moderately sensitive measurement of estradiol: -Evaluation of hypogonadism and oligo-amenorrhea in females -Assessing ovarian status, including follicle development, for assisted reproduction protocols (eg, in vitro fertilization) -In conjunction with luteinizing hormone measurements, monitoring of estrogen replacement therapy in hypogonadal premenopausal women -Evaluation of feminization, including gynecomastia, in males -Diagnosis of estrogen-producing neoplasms in males and, to a lesser degree, females -As part of the diagnosis and workup of precocious and delayed puberty in females, and, to a lesser degree, males -As part of the diagnosis and workup of suspected disorders of sex steroid metabolism (eg, aromatase deficiency and 17 alpha-hydroxylase deficiency) -As an adjunct to clinical assessment, imaging studies and bone mineral density measurement in the fracture risk assessment of postmenopausal women, and, to a lesser degree, older men -Monitoring low-dose female hormone replacement therapy in postmenopausal women -Monitoring antiestrogen therapy (eg, aromatase inhibitor therapy)

Interpretation:

Estradiol (E2) levels below the premenopausal reference range in young females indicate hypogonadism. If luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels are elevated, primary gonadal failure is diagnosed. The main causes are genetic (eg, Turner syndrome, familial premature ovarian failure), autoimmune (eg, autoimmune ovarian failure, possibly as part of autoimmune polyglanular endocrine failure syndrome type II), and toxic (eg, related to chemotherapy or radiation therapy for malignant disease). If LH/FSH levels are low or inappropriately "normal," a diagnosis of hypogonadotrophic hypogonadism is made. This can have functional causes, such as starvation, overexercise, severe physical or emotional stress, and heavy drug and/or alcohol use. It also can be caused by organic disease of the hypothalamus or pituitary. Further workup is usually necessary, typically including measurement of pituitary hormones (particularly prolactin), and possibly imaging. Irregular or absent menstrual periods with normal or high E2 levels (and often high estrone: E1 levels
are indicative of possible polycystic ovarian syndrome, androgen producing tumors, or estrogen producing tumors. Further workup is required and usually includes measurement of total and bioavailable testosterone, androstenedione, dehydroepiandrosterone (sulfate), sex hormone-binding globulin, and possibly imaging. E2 levels change during the menstrual cycle, as follows: -Post-menses, levels may be as low as 15 pg/mL. -Levels then rise during the follicular phase to a preovulatory peak, typically in the 300+ pg/mL range. -Levels fall in the luteal phase. -Menses typically occur when E2 levels are in the 50 to 100 pg/mL range. E2 analysis may be helpful in establishing time of ovulation and optimal time for conception. Optimal time for conception is within 48 to 72 hours following the midcycle E2 peak. Serial specimens must be drawn over several days to evaluate baseline and peak total estrogen (E1 + E2) levels. Low baseline levels and a lack of rise, as well as persistent high levels without midcycle rise, are indicative of anovulatory cycles. For determining the timing of initiation of ovarian stimulation in vitro fertilization studies, low levels (around 30 pg/mL) before stimulation, are critical, as higher values often are associated with poor stimulation cycles. Estrogen replacement in reproductive-age women should aim to mimic natural estrogen levels as closely as possible. E2 levels should be within the reference range for premenopausal women. LH/FSH should be within the normal range, and E2 levels should ideally be higher than E1 levels. The current recommendations for postmenopausal female hormone replacement are to administer therapy in the smallest beneficial doses for as briefly as possible. Ideally, E2 and E1 levels should be held below, or near, the lower limit of the premenopausal female reference range. Postmenopausal women and older men in the lowest quartile of E2 levels are at increased risk of osteoporotic fractures. E2 levels are typically less than 5 pg/mL in these patients. Antiestrogen therapy with central or peripheral acting agents that are not pure receptor antagonists usually aims for complete suppression of E2 production, and in the case of aromatase inhibitors, complete E1 and E2 suppression. Gynecomastia or other signs of feminization in males may be due to an absolute or relative (in relation to androgens) surplus of estrogens. Gynecomastia is common during puberty in boys. Unless E1, E2, or testosterone levels exceed the adult male reference range, the condition is usually not due to hormonal disease (though it sometimes may still result in persistent breast tissue, which later needs to be surgically removed). For adults with gynecomastia, the workup should include testosterone and adrenal androgen measurements, in addition to E2 and E1 measurements. Causes for increased E1 or E2 levels include: -High androgen levels caused by tumors or androgen therapy (medical or sport performance enhancing), with secondary elevations in E1 and E2 due to aromatization. -Obesity with increased tissue production of E1. -Decreased E1 and E2 clearance in liver disease. -Estrogen producing tumors. -Estrogen ingestion. Normal male E1 and E2 levels also may be associated with feminization or gynecomastia, if bioavailable testosterone levels are low due to primary/secondary testicular failure. This may occur, for example, when patients are receiving antiandrogen therapy or other drugs with antiandrogenic effects (eg, spironolactone, digitalis preparations). The gonadotrophin-releasing hormone stimulation test remains the central part of the workup for precocious puberty. However, baseline sex steroid and gonadotrophin measurements also are important. Prepubertal girls have E2 levels below 10 pg/mL (most <5 pg/mL). Levels in prepubertal boys are less than half the levels seen in girls. LH/FSH are very low or undetectable. E1 levels also are low, but may rise slightly in obese children after onset of adrenarche. E2, which is produced in the gonads, should remain low in these children. In true precocious puberty, both E2 and LH/FSH levels are elevated above the prepubertal range. Elevation of E2 or E1 alone suggests pseudo-precocious puberty, possibly due to a sex steroid-producing tumor. In delayed puberty, estrogens and gonadotrophins are in the prepubertal range. A rise over time predicts the spontaneous onset of puberty. Persistently low estrogens and elevated gonadotrophins suggest primary ovarian failure, while low gonadotrophins suggest hypogonadotropic hypogonadism. In this latter case, Kallmann syndrome (or related disorders) or hypothalamic/pituitary tumors should be excluded in well-nourished children. Inherited disorders of sex steroid metabolism are usually associated with production abnormalities of other steroids, most notably a lack of cortisol. Aromatase deficiency is not associated with cortisol abnormalities and usually results in some degree of masculinization in affected females, as well as primary failure of puberty. Males may show delayed puberty and delayed epiphyseal closure, as well as low bone-density. E2 and E1 levels are very low or undetectable. Various forms of testicular feminization are due to problems in androgen signaling pathways and are associated with female (or feminized) phenotypes in genetic males. E2 and E1 levels are above the male reference range, usually within the female reference range, and testosterone levels are very high. See Steroid Pathways in Special Instructions.

**Reference Values:**

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<thead>
<tr>
<th>Tanner Stages</th>
<th>Mean Age</th>
<th>Reference Range</th>
</tr>
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Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
### Clinical References:


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### Clinical Information: Estriol, Unconjugated, Serum

**Clinical Information:** Estrogens are involved in development and maintenance of the female phenotype, germ cell maturation, and pregnancy. They also are important in many other nongender-specific functions in men and women. These include growth, nervous system maturation, bone metabolism, and endothelial responsiveness. There are 3 major biologically active estrogens in humans: estrone (E1), estradiol (E2), and estriol (E3). Like all members of the steroid hormone family, they diffuse into cells and bind to specific nuclear receptors, which in turn alter gene transcription in a...
tissue specific manner. E2 is the most potent natural human estrogen, closely followed by E1, while E3 possess only 20% of the E2 affinity for the estrogen receptor. In men and nonpregnant women, E1 and E2 are formed from the androgenic steroids androstenedione and testosterone, respectively. E3 is derived largely through conversion of E2, and to a lesser degree from 16α-metabolites of E1. E2 and E1 can also be converted into each other, and both can be inactivated via hydroxylation and conjugation. During pregnancy E3 becomes the dominant estrogen. The fetal adrenal gland secretes dehydroepiandrosterone-sulfate (DHEAS), which is converted to E3 in the placenta and diffuses into the maternal circulation. The half-life of unconjugated E3 (uE3) in the maternal blood system is 20 to 30 minutes, since the maternal liver quickly conjugates E3 to make it more water soluble for urinary excretion. E3 levels increase throughout the course of pregnancy, peaking at term. Measurement of serum E2 and E1 levels is an integral part of assessment of reproductive function in females, and also has applications in both men and women in osteoporosis risk assessment and monitoring of female hormone replacement therapy. By contrast, with the exception of epidemiological studies assessing breast cancer risk and other scientific studies, the main value of E3 measurements is in the diagnosis of maternal-fetal diseases. In those settings, measurement of serum uE3 levels plays a major role.

Decreased second trimester uE3 has been shown to be a marker for Down and trisomy-18 syndromes. It also is low in cases of gross neural tube defects such as anencephaly. Based on these observations, uE3 has become a part of multiple marker prenatal biochemical screening, together with alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), and inhibin-A measurements (QUAD / Quad Screen (Second Trimester) Maternal, Serum). Low levels of uE3 also have been associated with pregnancy loss, Smith-Lemli-Opitz syndrome (defect in cholesterol biosynthesis), X-linked ichthyosis and contiguous gene syndrome (placental sulfatase deficiency disorders), aromatase deficiency, and primary or secondary fetal adrenal insufficiency. High levels of uE3, or sudden increases in maternal uE3 levels, are a marker of pending labor. The rise occurs approximately 4 weeks before onset of labor. Since uE3 has been shown to be more accurate than clinical assessment in predicting labor onset, there is increasing interest in its use in assessment of preterm labor risk. High maternal serum uE3 levels may also be occasionally observed in various forms of congenital adrenal hyperplasia.

**Useful For:** A part of the SEQF/ Sequential Maternal Screening, Part 2, Serum and QUAD / Quad Screen (Second Trimester) Maternal, Serum in biochemical second trimester or cross-trimester screening for Down syndrome and trisomy 18 syndrome A marker of fetal demise An element in the prenatal diagnosis of disorders of fetal steroid metabolism, including Smith-Lemli-Opitz syndrome, X-linked ichthyosis and contiguous gene syndrome (placental sulfatase deficiency disorders), aromatase deficiency, primary or secondary fetal adrenal insufficiency, and various forms of congenital adrenal hyperplasia Assessment of preterm labor risk Epidemiological studies of breast cancer risk in conjunction with measurement of estrone, estradiol, and various metabolites Assessing estrogen metabolism, estrogen and estrogen-like medications, and other endogenous or exogenous factors impacting on estrogen metabolism in the context of other basic scientific and clinical studies

**Interpretation:** In the context of the quad test, the measured unconjugated E3 (uE3) value forms part of a complex, multivariate risk calculation formula, using maternal age, gestational stage, and other demographic information, in addition to the results of the 4 tested markers, for Down syndrome, trisomy 18 syndrome, and neural tube defect risk calculations. A serum uE3 <0.3 multiples of the gestational age median in women who otherwise screen negative in the quad test, indicates the possibility of fetal demise, Smith-Lemli-Opitz syndrome, X-linked ichthyosis or contiguous gene syndrome, aromatase deficiency, or primary or secondary fetal adrenal insufficiency. An elevated serum or uE3 >3.0 multiples of the gestational age mean, or with an absolute value of >2.1 ng/mL, can be an indication of pending labor or fetal congenital adrenal hyperplasia. In the context of assessment of a patient deemed at risk of preterm labor, a single serum or uE3 measurement within the above cutoffs, has a negative predictive value of labor onset (ie, labor unlikely within the next 4 weeks) of 98% in low-risk populations and of 96% in high-risk populations. Measurements of serum uE3 performed in the context of epidemiological or other basic or clinical scientific studies need to be interpreted in the context of those studies. No overall guidelines can be given.

**Reference Values:**

Males: <0.07 ng/mL
Females: <0.08 ng/mL

For SI unit Reference Values, see
**Estrogen Receptor (ER) Immunostain, Technical Component Only**

**Clinical Information:** Estrogen receptor alpha protein expression is limited to normal and neoplastic tissues related to the reproductive system (breast, cervix, endometrium, uterus, ovary, and prostate).

**Useful For:** Qualitative detection of estrogen receptor alpha protein in a diagnostic setting

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**Estrogen Receptor 1 (ESR1) Mutation Analysis, Tumor**

**Clinical Information:** The ESR1 gene encodes an estrogen receptor that regulates cell growth through activation of downstream signaling pathways upon binding of estrogen. Tumors demonstrating estrogen receptor expression (ER-positive) are candidates for endocrine therapy such as selective estrogen receptor modulators (SERM) and aromatase inhibitors. ESR1 mutations are rarely observed in primary tumors; however, mutations in the ligand-binding domain of ESR1 have been reported at a higher frequency in ER-positive metastatic breast tumors. Preclinical data suggests that ESR1 mutations mitigate resistance to aromatase inhibitors and decrease sensitivity to SERMs and estrogen-receptor downregulators. Studies also suggest that ESR1 mutations are an independent indicator of poor prognosis. This test assesses for somatic mutations in the ligand-binding domain of the ESR1 gene associated with acquired resistance to endocrine therapy (ie, aromatase inhibitors) in patients with ER-positive metastatic breast cancer.

**Useful For:** Assisting in the clinical management of patients with metastatic breast cancer by identifying tumors with evolving resistance to endocrine therapy Stratifying prognosis of metastatic breast cancer

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

**ERBE1**

**Estrogen Receptor Beta-1 Immunostain, Technical Component Only**

**Clinical Information:** This test is intended to identify the presence of estrogen receptor beta 1 (ER-beta 1) protein. ER-beta 1 is a member of the nuclear receptor superfamily of transcription factors and is the product of the ESR2 gene on chromosome 14q22-24. Unlike ER-alpha, ER-beta 1 is highly expressed in normal breast epithelium but expression is reduced in many precancerous and cancerous breast tumors. ER-beta 1 is expressed in 30% to 40% of triple negative breast cancers and is associated with improved outcomes in ER-alpha positive tamoxifen treated patients.

**Useful For:** Detection of estrogen receptor-beta 1 protein levels in cancer, including triple-negative breast cancer

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**ERPR**

**Estrogen/Progesterone Receptor, Semi-Quantitative Immunohistochemistry, Manual**

**Clinical Information:** The steroid hormone receptors, estrogen receptor (ER) and progesterone receptor (PR), are commonly used in the management of women with breast cancer. ER and PR status provide an indication of prognosis and of the potential benefit from hormonal therapy. Generally, ER/PR-positive tumors are more likely to respond to endocrine therapy and have a better prognosis, stage-for-stage, than receptor-negative tumors. While the test can be performed on any formalin-fixed, paraffin-embedded tissue, it is infrequently used for non-breast cancer specimens.

**Useful For:** Guiding decisions on hormonal therapy in patients with breast carcinomas
Interpretation: Immunoperoxidase-stained slides are examined microscopically by the consulting anatomic pathologist and interpreted as negative (<1% reactive cells), or positive. The percent of reactive cells is provided in the report.

Reference Values:
- Negative: <1% reactive cells
- Positive: >1% reactive cells

Clinical References:

Estrogens, Estrone (E1) and Estradiol (E2), Fractionated, Serum

Clinical Information: Estrogens are involved in development and maintenance of the female phenotype, germ cell maturation, and pregnancy. They also are important for many other, non-gender-specific processes, including growth, nervous system maturation, bone metabolism/remodeling, and endothelial responsiveness. The 2 major biologically active estrogens in nonpregnant humans are estrone (E1) and estradiol (E2). A third bioactive estrogen, estriol (E3), is the main pregnancy estrogen, but plays no significant role in nonpregnant women or men. E2 is produced primarily in ovaries and testes by aromatization of testosterone. Small amounts are produced in the adrenal glands and some peripheral tissues, most notably fat. By contrast, most of the circulating E1 is derived from peripheral aromatization of androstenedione (mainly adrenal). E2 and E1 can be converted into each other, and both can be inactivated via hydroxylation and conjugation. E2 demonstrates 1.25 to 5 times the biological potency of E1. E2 circulates at 1.5 to 4 times the concentration of E1 in premenopausal, nonpregnant women. E2 levels in men and postmenopausal women are much lower than in nonpregnant women, while E1 levels differ less, resulting in a reversal of the premenopausal E2:E1 ratio. E2 levels in premenopausal women fluctuate during the menstrual cycle. They are lowest during the early follicular phase. E2 levels then rise gradually until 2 to 3 days before ovulation, at which stage they start to increase much more rapidly and peak just before the ovulation-inducing luteinizing hormone/follicle stimulating hormone surge at 5 to 10 times the early follicular levels. This is followed by a modest decline during the ovulatory phase. E2 levels then gradually increase again until the midpoint of the luteal phase and thereafter decline to trough, early follicular levels. Measurement of serum E2 forms an integral part of the assessment of reproductive function in females, including assessment of infertility, oligo-amenorrhea, and menopausal status. In addition, it is widely used for monitoring ovulation induction, as well as during preparation for in vitro fertilization. For these applications E2 measurements with modestly sensitive assays suffice. However, extra sensitive E2 assays, simultaneous measurement of E1, or both are needed in a number of other clinical situations. These include inborn errors of sex steroid metabolism, disorders of puberty, estrogen deficiency in men, fracture risk assessment in menopausal women, and increasingly, therapeutic drug monitoring, either in the context of low-dose female hormone replacement therapy or antiestrogen treatment.

Useful For: Simultaneous high-sensitivity determination of serum estrone and estradiol levels

Situations requiring either higher sensitivity estradiol measurement, estrone measurement, or both, including:
- As part of the diagnosis and workup of precocious and delayed puberty in females and, to a lesser degree, males
- As part of the diagnosis and workup of suspected disorders of sex steroid metabolism, eg, aromatase deficiency and 17 alpha-hydroxylase deficiency
- As an adjunct to clinical assessment, imaging studies, and bone mineral density measurement in the fracture risk assessment of postmenopausal women and, to a lesser degree, older men
- Monitoring low-dose female hormone replacement therapy in postmenopausal women
- Monitoring antiestrogen therapy (eg, aromatase inhibitor therapy)

Applications that require moderately sensitive measurement of estradiol including:
- Evaluation of hypogonadism and oligo-amenorrhea in females
- Assessing ovarian status, including follicle development, for assisted reproduction protocols (eg, in vitro fertilization)

In conjunction with...
luteinizing hormone measurements, monitoring of estrogen replacement therapy in hypogonadal premenopausal women Evaluation of feminization, including gynecomastia, in males Diagnosis of estrogen-producing neoplasms in males, and, to a lesser degree, females

**Interpretation:** Estradiol (E2) levels below the premenopausal reference range in young females indicate hypogonadism. If luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels are elevated, primary gonadal failure is diagnosed. The main causes are genetic (eg, Turner syndrome, familial premature ovarian failure), autoimmune (eg, autoimmune ovarian failure, possibly as part of autoimmune polyglandular endocrine failure syndrome type II), and toxic (eg, related to chemotherapy or radiation therapy for malignant disease). If LH/FSH levels are low or inappropriately "normal," a diagnosis of hypogonadotrophic hypogonadism is made. This can have functional causes, such as starvation, overexercise, severe physical or emotional stress, and heavy drug and/or alcohol use. It also can be caused by organic disease of the hypothalamus or pituitary. Further work-up is usually necessary, typically including measurement of pituitary hormones (particularly prolactin), and possibly imaging. Irregular or absent menstrual periods with normal or high E2 levels (and often high estrone [E1] levels) are indicative of possible polycystic ovarian syndrome, androgen producing tumors, or estrogen producing tumors. Further work-up is required and usually includes measurement of total and bioavailable testosterone, androstenedione, dehydroepiandrosterone (sulfate), sex hormone-binding globulin, and possibly imaging. E2 analysis may be helpful in establishing time of ovulation and optimal time for conception. Optimal time for conception is within 48 to 72 hours following the midcycle E2 peak. Serial specimens must be drawn over several days to evaluate baseline and peak total estrogen (E1 + E2) levels. Low baseline levels and a lack of rise, as well as persistent high levels without midcycle rise are indicative of anovulatory cycles. For determining the timing of initiation of ovarian stimulation in in vitro fertilization studies, low levels (around 30 pg/mL) before stimulation are critical, as higher values often are associated with poor stimulation cycles. Estrogen replacement in reproductive age women should aim to mimic natural estrogen levels as closely as possible. E2 levels should be within the reference range for premenopausal women. LH/FSH should be within the normal range, and E2 levels should ideally be higher than E1 levels. The current recommendations for postmenopausal female hormone replacement are to administer therapy in the smallest beneficial doses for as briefly as possible. Ideally, E2 and E1 levels should be held below, or near, the lower limit of the premenopausal female reference range. Postmenopausal women and older men in the lowest quartile of E2 levels are at increased risk of osteoporotic fractures. E2 levels are typically less than 5 pg/mL. Antiestrogen therapy with central or peripheral acting agents that are not pure receptor antagonists usually aims for complete suppression of E2 production, and in the case of aromatase inhibitors, complete E1 and E2 suppression. Gynecomastia or other signs of feminization in males may be due to an absolute or relative (in relation to androgens) surplus of estrogens. Gynecomastia is common during puberty in boys. Unless E1, E2, or testosterone levels exceed the adult male reference range, the condition is usually not due to hormonal disease (though it sometimes may still result in persistent breast tissue, which later needs to be surgically removed). For adults with gynecomastia, the workup should include testosterone and adrenal androgen measurements, in addition to E2 and E1 measurements. Causes for increased E1 or E2 levels include: -High androgen levels caused by tumors or androgen therapy (medical or sport performance enhancing), with secondary elevations in E1 and E2 due to aromatization -Obesity with increased tissue production of E1 -Decreased E1 and E2 clearance in liver disease -Estrogen producing tumors -Estrogen ingestion Normal male E1 and E2 levels also may be associated with feminization or gynecomastia, if bioavailable testosterone levels are low due to primary/secondary testicular failure. This may occur, for example, when patients are receiving antiandrogen therapy or other drugs with antiandrogenic effects (eg, spironolactone, digitalis preparations). The gonadotrophin-releasing hormone (GnRH) stimulation test remains the central part of the workup for precocious puberty. However, baseline sex steroid and gonadotrophin measurements also are important. Prepubertal girls have E2 levels less than 10 pg/mL (most 5 pg/mL). Levels in prepubertal boys are less than half the levels seen in girls. LH/FSH are very low or undetectable. E1 levels also are low, but may rise slightly, in obese children after onset of adrenarche. E2, which is produced in the gonads, should remain low in these children. In true precocious puberty, both E2 and LH/FSH levels are elevated above the prepubertal range. Elevation of E2 or E1 alone suggests pseudo precocious puberty, possibly due to a sex steroid-producing tumor. In delayed puberty, estrogens and gonadotropins are in the prepubertal range. A rise over time predicts the spontaneous onset of puberty. Persistently low estrogens and elevated gonadotrophins suggest primary ovarian failure, while low gonadotrophins suggest hypogonadotrophic hypogonadism. In this latter case, Kallman syndrome (or related disorders) or hypothalamic/pituitary tumors should be excluded in well-nourished children. Inherited disorders of sex
steroid metabolism are usually associated with production abnormalities of other steroids, most notably a lack of cortisol. Aromatase deficiency is not associated with cortisol abnormalities and usually results in some degree of masculinization in affected females, as well as primary failure of puberty. Males may show delayed puberty and delayed epiphyseal closure, as well as low bone-density. E2 and E1 levels are very low or undetectable. Various forms of testicular feminization are due to problems in androgen signaling pathways and are associated with female (or feminized) phenotypes in genetic males. E2 and E1 levels are above the male reference range, usually within the female reference range, and testosterone levels are very high.

**Reference Values:**

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<tr>
<th>Tanner Stages#</th>
<th>Mean Age</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (&gt;14 days and prepubertal)</td>
<td>7.1 years</td>
<td>Undetectable-16 pg/mL</td>
</tr>
<tr>
<td>Stage II</td>
<td>11.5 years</td>
<td>Undetectable-22 pg/mL</td>
</tr>
<tr>
<td>Stage III</td>
<td>13.6 years</td>
<td>10-25 pg/mL</td>
</tr>
<tr>
<td>Stage IV</td>
<td>15.1 years</td>
<td>10-46 pg/mL</td>
</tr>
<tr>
<td>Stage V</td>
<td>18 years</td>
<td>10-60 pg/mL #Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years. For boys there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18. Females</td>
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<td>10.5 years</td>
<td>10-33 pg/mL</td>
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<tr>
<td>Stage III</td>
<td>11.6 years</td>
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<td>Stage IV</td>
<td>12.3 years</td>
<td>16-77 pg/mL</td>
</tr>
<tr>
<td>Stage V</td>
<td>14.5 years</td>
<td>17-200 pg/mL #Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18. <em>The reference ranges for children are based on the published literature,(1,2) cross-correlation of our assay with assays used to generate the literature data and on our data for young adults. ADULTS Males: 10-60 pg/mL. Females Premenopausal: 17-200 pg/mL. Postmenopausal: 7-40 pg/mL. Conversion factor E1: pg/mL x 3.704=pmol/L (molecular weight=270) ESTRADIOL (E2) CHILDREN</em> 1-14 days: Estradiol levels in newborns are very elevated at birth but will fall to prepubertal levels within a few days. Males</td>
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<td>Undetectable-6 pg/mL</td>
</tr>
<tr>
<td>Stage III</td>
<td>13.6 years</td>
<td>Undetectable-26 pg/mL</td>
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</table>
Stage IV 15.1 years Undetectable-38 pg/mL
Stage V 18 years 10-40 pg/mL #Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/- 2) years. For boys there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18. Females

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<td>Stage IV</td>
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</tbody>
</table>
| Stage V       | 14.5 years | 15-350 pg/mL** #Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/- 2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18. *The reference ranges for children are based on the published literature,(1,2) cross-correlation of our assay with assays used to generate the literature data and on our data for young adults. ADULTS Males: 10-40 pg/mL Females Premenopausal: 15-350 pg/mL** Postmenopausal: E2 levels vary widely through the menstrual cycle. Conversion factor E2: pg/mL x 3.676=pmol/L (molecular weight=272) For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.


**E1 81418 Estrone, Serum**

**Clinical Information:** Estrogens are involved in development and maintenance of the female phenotype, germ cell maturation, and pregnancy. They also are important for many other, nongender-specific processes, including growth, nervous system maturation, bone metabolism/remodeling, and endothelial responsiveness. The 2 major biologically active estrogens in nonpregnant humans are estrone (E1) and estradiol (E2). A third bioactive estrogen, estriol (E3), is the main pregnancy estrogen, but plays no significant role in nonpregnant women or men. E2 is produced primarily in ovaries and testes by aromatization of testosterone. Small amounts are produced in the adrenal glands and some peripheral tissues, most notably fat. By contrast, most of the circulating E1 is derived from peripheral aromatization of androstenedione (mainly adrenal). E2 and E1 can be converted into each other, and both can be inactivated via hydroxylation and conjugation. E2 demonstrates 1.25-5 times the biological potency of E1. E2 circulates at 1.5-4 times the concentration of E1 in premenopausal, nonpregnant women. E2 levels in men and postmenopausal women are much lower than in nonpregnant
women, while E1 levels differ less, resulting in a reversal of the premenopausal E2:E1 ratio. E2 levels in premenopausal women fluctuate during the menstrual cycle. They are lowest during the early follicular phase. E2 levels then rise gradually until 2 to 3 days before ovulation, at which stage they start to increase much more rapidly and peak just before the ovulation-inducing luteinizing hormone/follicle stimulating hormone surge at 5 to 10 times the early follicular levels. This is followed by a modest decline during the ovulatory phase. E2 levels then increase again gradually until the midpoint of the luteal phase and thereafter decline to trough, early follicular levels. Measurement of serum E2 forms an integral part of the assessment of reproductive function in females, including assessment of infertility, oligo-amenorrhea and menopausal status. In addition, it is widely used for monitoring ovulation induction, as well as during preparation for in vitro fertilization. For these applications E2 measurements with modestly sensitive assays suffice. However, extra sensitive E2 assays or simultaneous measurement of E1, or both are needed in a number of other clinical situations. These include inborn errors of sex steroid metabolism, disorders of puberty, estrogen deficiency in men, fracture risk assessment in menopausal women, and increasingly, therapeutic drug monitoring, either in the context of low-dose female hormone replacement therapy or antiestrogen treatment. See Steroid Pathways in Special Instructions.

**Useful For:** As part of the diagnosis and workup of precocious and delayed puberty in females and, to a lesser degree, males As part of the diagnosis and workup of suspected disorders of sex steroid metabolism (eg, aromatase deficiency and 17 alpha-hydroxylase deficiency) As an adjunct to clinical assessment, imaging studies and bone mineral density measurement in the fracture risk assessment of postmenopausal women, and, to a lesser degree, older men Monitoring low-dose female hormone replacement therapy in postmenopausal women Monitoring antiestrogen therapy (eg, aromatase inhibitor therapy)

**Interpretation:** Irregular or absent menstrual periods with normal or high E2 levels (and often high E1 levels) are indicative of possible polycystic ovarian syndrome, androgen producing tumors, or estrogen producing tumors. Further work-up is required and usually includes measurement of total and bioavailable testosterone, androstenedione, dehydroepiandrosterone (sulfate), sex hormone-binding globulin, and possibly imaging. Estrogen replacement in reproductive age women should aim to mimic natural estrogen levels as closely as possible. E2 levels should be within the reference range for premenopausal women, luteinizing hormone/follicle-stimulating hormone (LH/FSH) should be within the normal range, and E2 levels should ideally be higher than E1 levels. Postmenopausal women and older men in the lowest quartile of E2 levels are at increased risk of osteoporotic fractures. E2 levels are typically less than 5 pg/mL in these patients. The current recommendations for postmenopausal female hormone replacement are to administer therapy in the smallest beneficial doses for as briefly as possible. Ideally, E2 and E1 levels should be held below, or near, the lower limit of the premenopausal female reference range. Antiestrogen therapy with central or peripheral acting agents that are not pure receptor antagonists usually aims for complete suppression of E2 production, and in the case of aromatase inhibitors, complete E1 and E2 suppression. Gynecomastia or other signs of feminization in males may be due to an absolute or relative (in relation to androgens) surplus of estrogens. Gynecomastia is common during puberty in boys. Unless E1, E2, or testosterone levels exceed the adult male reference range, the condition is usually not due to hormonal disease (though it sometimes may still result in persistent breast tissue, which later needs to be surgically removed). For adults with gynecomastia, the work-up should include testosterone and adrenal androgen measurements, in addition to E2 and E1 measurements. Causes for increased E1 or E2 levels include: - High androgen levels caused by tumors or androgen therapy (medical or sport performance enhancing), with secondary elevations in E1 and E2 due to aromatization - Obesiy with increased tissue production of E1 - Decreased E1 and E2 clearance in liver disease - Estrogen producing tumors - Estrogen ingestion. Normal male E1 and E2 levels also may be associated with feminization or gynecomastia if bioavailable testosterone levels are low due to primary/secondary testicular failure. This may occur, for example, when patients are receiving antiandrogen therapy or other drugs with antiandrogenic effects (eg, spironolactone, digitalis preparations). The gonadotrophin-releasing hormone stimulation test remains the central part of the work-up for precocious puberty. However, baseline sex steroid and gonadotrophin measurements also are important. Prepubertal girls have E2 levels less than 10 pg/mL (most <5 pg/mL). Levels in prepubertal boys are less than half the levels seen in girls. LH/FSH are very low or undetectable. E1 levels also are low, but may rise slightly in obese children after onset of adrenarche. E2, which is produced in the gonads, should remain low in these children. In true precocious puberty, both E2 and LH/FSH levels are elevated above the prepubertal range. Elevation of E2 or E1 alone
suggests pseudo precocious puberty, possibly due to a sex steroid-producing tumor. In delayed puberty, estrogens and gonadotrophins are in the prepubertal range. A rise over time predicts the spontaneous onset of puberty. Persistently low estrogens and elevated gonadotrophins suggest primary ovarian failure, while low gonadotrophins suggest hypogonadotrophic hypogonadism. In this latter case, Kallman syndrome (or related disorders) or hypothalamic/pituitary tumors should be excluded in well-nourished children. Inherited disorders of sex steroid metabolism are usually associated with production abnormalities of other steroids, most notably a lack of cortisol. Aromatase deficiency is not associated with cortisol abnormalities and usually results in some degree of masculinization in affected females, as well as primary failure of puberty. Males may show delayed puberty and delayed epiphyseal closure, as well as low bone-density. E2 and E1 levels are very low or undetectable. Various forms of testicular feminization are due to problems in androgen signaling pathways and are associated with female (or feminized) phenotypes in genetic males. E2 and E1 levels are above the male reference range, usually within the female reference range, and testosterone levels are very high. See Steroid Pathways in Special Instructions.

Reference Values:

<table>
<thead>
<tr>
<th>Tanner Stages#</th>
<th>Mean Age</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (&gt;14 days and prepubertal)</td>
<td>7.1 years</td>
<td>Undetectable-16 pg/mL</td>
</tr>
<tr>
<td>Stage II</td>
<td>11.5 years</td>
<td>Undetectable-22 pg/mL</td>
</tr>
<tr>
<td>Stage III</td>
<td>13.6 years</td>
<td>10-25 pg/mL</td>
</tr>
<tr>
<td>Stage IV</td>
<td>15.1 years</td>
<td>10-46 pg/mL</td>
</tr>
<tr>
<td>Stage V</td>
<td>18 years</td>
<td>10-60 pg/mL #Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/- 2) years. For boys there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.</td>
</tr>
</tbody>
</table>

Females

<table>
<thead>
<tr>
<th>Tanner Stages#</th>
<th>Mean Age</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (&gt;14 days and prepubertal)</td>
<td>7.1 years</td>
<td>Undetectable-29 pg/mL</td>
</tr>
<tr>
<td>Stage II</td>
<td>10.5 years</td>
<td>10-33 pg/mL</td>
</tr>
<tr>
<td>Stage III</td>
<td>11.6 years</td>
<td>15-43 pg/mL</td>
</tr>
<tr>
<td>Stage IV</td>
<td>12.3 years</td>
<td>16-77 pg/mL</td>
</tr>
<tr>
<td>Stage V</td>
<td>14.5 years</td>
<td>17-200 pg/mL #Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/- 2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18. *The reference ranges for children are based on the published literature(1,2), cross-correlation of our assay with assays used to generate the literature data and on our data for young adults. ADULTS Males: 10-60 pg/mL. Females Premenopausal: 17-200 pg/mL. Postmenopausal: 7-40 pg/mL. Conversion factor E1: pg/mL x 3.704=pmol/L (molecular weight=270) For SI unit Reference Values, see <a href="https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html">https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html</a>.</td>
</tr>
</tbody>
</table>

Ethanol, Blood

**Clinical Information:** Ethanol is the single most important substance of abuse in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. Ethanol acts on cerebral functions as a depressant similar to general anesthetics. This depression causes most of the typical symptoms such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment becomes progressively increased. In most jurisdictions in the United States, the level of prima facie evidence of being under the influence of alcohol for purposes of driving a motor vehicle is 80 mg/dL.

**Useful For:** Detection of ethanol (ethyl alcohol) in blood to document prior consumption or administration of ethanol. Quantification of the concentration of ethanol in blood correlates directly with the degree of intoxication.

**Interpretation:** The presence of ethanol in blood at concentrations above 30 mg/dL (>0.03% or g/dL) is generally accepted as a strong indicator of the use of an alcohol-containing beverage. Blood ethanol levels above 50 mg/dL (>0.05%) are frequently associated with a state of increased euphoria. Blood ethanol level above 80 mg/dL (>0.08%) exceeds Minnesota's legal limit for driving a motor vehicle. These levels are frequently associated with loss of manual dexterity and with sedation. A blood alcohol level of 400 mg/dL (> or =0.4%) or higher may be lethal as normal respiration may be depressed below the level necessary to maintain life. The blood ethanol level is also useful in diagnosis of alcoholism. A patient who chronically consumes ethanol will develop a tolerance to the drug, and requires higher levels than described above to achieve various states of intoxication. An individual who can function in a relatively normal manner with a blood ethanol level above 150 mg/dL (>0.15%) is highly likely to have developed a tolerance to the drug achieved by high levels of chronic intake.

**Reference Values:**

- Not detected (Positive results are quantified.)
- Limit of detection: 10 mg/dL (0.01 g/dL)
- Legal limit of intoxication is 80 mg/dL (0.08 g/dL).
- Toxic concentration is dependent upon individual usage history.
- Potentially lethal concentration: > or =400 mg/dL (0.4 g/dL)


Ethanol, Chain of Custody, Blood

**Clinical Information:** Ethanol is the single most important substance of abuse in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. Ethanol acts on cerebral functions as a depressant similar to general anesthetics. This depression causes most of the typical symptoms such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment becomes progressively increased. In most jurisdictions in the United States, the level of prima facie evidence of being under the influence of alcohol for purposes of driving a motor vehicle is 80 mg/dL. Chain of custody is required whenever the results of testing could be used in a court of law. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen...
tampering would be limited. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** All testing is performed under strict chain of custody Detection of ethanol (ethyl alcohol) in blood to document prior consumption or administration of ethanol Quantification of the concentration of ethanol in blood correlates directly with degree of intoxication

**Interpretation:** The presence of ethanol in blood at concentrations greater than 30 mg/dL (>0.03% or g/dL) is generally accepted as a strong indicator of the use of an alcohol-containing beverage. Blood ethanol levels above 50 mg/dL (>0.05%) are frequently associated with a state of increased euphoria. Blood ethanol level above 80 mg/dL (>0.08%) exceeds Minnesota’s legal limit for driving a motor vehicle. These levels are frequently associated with loss of manual dexterity and with sedation. A blood alcohol level of 400 mg/dL (> or =0.4%) or more may be lethal as normal respiration may be depressed below the level necessary to maintain life. The blood ethanol level is also useful in diagnosis of alcoholism. A patient who chronically consumes ethanol will develop a tolerance to the drug, and requires higher levels than described above to achieve various states of intoxication. An individual who can function in a relatively normal manner with a blood ethanol level above 150 mg/dL (>0.15%) is highly likely to have developed a tolerance to the drug achieved by high levels of chronic intake.

**Reference Values:**
Not detected (Positive results are quantified.)
Limit of detection: 10 mg/dL (0.01 g/dL)
Legal limit of intoxication is 80 mg/dL (0.08 g/dL).
Toxic concentration is dependent upon individual usage history.
Potentially lethal concentration: > or =400 mg/dL (0.4 g/dL)


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**ETHNL 37040**

**Ethanol, Serum**

**Clinical Information:** Ethanol is the single most important substance of abuse in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. Ethanol acts on cerebral functions as a depressant similar to general anesthetics. This depression causes most of the typical symptoms such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment becomes progressively increased. In most jurisdictions in the United States, the level of prima facie evidence of being under the influence of alcohol for purposes of driving a motor vehicle is a blood ethanol concentration 80 mg/dL (0.08 g/dL; 0.08%; 800 mcg/dL). In the context of medical/clinical assessment, serum is submitted for analysis. On average, the serum or serum concentration of the alcohols is 1.2-fold higher than blood. The serum would contain approximately 0.10 g/dL of ethanol in a blood specimen that contains 0.08 g/dL ethanol.

**Useful For:** Detection of ethanol (ethyl alcohol) in serum to document prior consumption or administration of ethanol Quantification of the concentration of ethanol in serum correlates with degree of intoxication.

**Interpretation:** The presence of ethanol in blood at concentrations greater than 30 mg/dL (>0.03%) is generally accepted as a strong indicator of the use of an alcohol-containing beverage. Blood ethanol levels greater than 50 mg/dL (>0.05%) are frequently associated with a state of increased euphoria. Blood ethanol levels greater than or equal to 80 mg/dL (> or =0.08%) exceeds Minnesota’s legal limit for driving a motor vehicle. These levels are frequently associated with loss of manual dexterity and with sedation. A blood alcohol level greater than or equal to 400 mg/dL (> or =0.4%) may be lethal as normal respiration may be depressed below the level necessary to maintain life. The blood ethanol level is also useful in diagnosis of alcoholism. A patient who chronically consumes ethanol will develop a tolerance to the drug and requires higher levels than described above to achieve various states of intoxication. An individual who can function in a relatively normal manner with a blood ethanol level greater than 150 mg/dL (>0.15%) is highly likely to have developed a tolerance to the drug achieved by high levels of chronic intake.
Reference Values:
<10 mg/dL
Legal limit of intoxication: > or =80 mg/dL
Critical value: > or =400 mg/dL


ETHSX
37041

Ethosuximide, Serum

Clinical Information: Ethosuximide (Zarontin) is used in the treatment of absence (petit mal) seizures, although valproic acid and methsuximide are used more frequently for this condition. Ethosuximide is completely absorbed from the gastrointestinal tract, reaching a peak plasma concentration in 1 to 7 hours. Approximately 10% to 20% of the drug is excreted unchanged in the urine; the remainder is metabolized by hepatic microsomal enzymes. The volume of distribution of ethosuximide is 0.7 L/kg, and its half-life is 40 to 50 hours. Little ethosuximide circulating in the blood is bound to protein. Ethosuximide produces a barbiturate-like toxicity, characterized by central nervous system and respiratory depression, nausea, and vomiting when the blood level is >150 mcg/mL.

Useful For: Monitoring therapy Determining compliance Assessing toxicity

Interpretation: Dosage is guided by blood levels; the therapeutic range for ethosuximide is 40 to 100 mcg/mL. Toxic concentration: >150 mcg/mL.

Reference Values:
Therapeutic: 40-100 mcg/mL
Critical value: >150 mcg/mL


ETHO
80449

Ethotoin (Peganone)

Reference Values:
Reference Range: 8.0 - 20.0 ug/mL

Please note: The therapeutic range for ethotoin is not well established.

Many patients respond well to ethotoin concentrations up to 60 ug/mL.

ETGS
63420

Ethyl Glucuronide Screen, Urine

Clinical Information: This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (ie, unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive rate due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The
immunoassay also has a false-negative rate to the antibody’s ability to cross-react with different
drugs in the class being screened for. Ethyl glucuronide is a direct metabolite of ethanol that is formed
by enzymatic conjugation of ethanol with glucuronic acid. Alcohol in urine is normally detected for
only a few hours, whereas ethyl glucuronide can be detected in the urine for 1 to 3 days.

**Useful For:** Screening for drug abuse involving alcohol

**Interpretation:** This assay only provides a preliminary analytical test result. A more specific
alternative method (ie, liquid chromatography-tandem mass spectrometry: LC-MS/MS) must be used to
obtain a confirmed analytical result. A positive result using the ethyl glucuronide screen indicates only the
potential presence of ethyl glucuronide and does not necessarily correlate with the extent of physiological
and psychological effects.

**Reference Values:**
- Negative
- Screening cutoff concentration:
  - Ethyl Glucuronide: 500 ng/mL

**Clinical References:**
GE, Weinmann W: Ethyl glucuronide--the direct ethanol metabolite on the threshold from science to
immunochemical test for the determination of ethyl glucuronide in serum and urine: comparison of
Weinmann W, Schaefer P, Thierauf A: Confirmatory analysis of ethyl glucuronide in urine by liquid
chromatography/electrospray ionization/tandem mass spectrometry according to forensic guidelines. J Am

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**Ethylene Glycol, Serum**

**Clinical Information:** Ethylene glycol, present in antifreeze products, may be ingested accidentally
or for the purpose of inebriation or suicide. Ethylene glycol itself is relatively nontoxic, and its initial
central nervous system (CNS) effects resemble those of ethanol. However, metabolism of ethylene glycol
by alcohol dehydrogenase results in the formation of a number of acid metabolites, including oxalic acid
and glycolic acid. These acid metabolites are responsible for much of the toxicity of ethylene glycol.
Three stages of ethylene glycol overdose occur. Within the first few hours after ingestion, there is
transient excitation followed by CNS depression. After a delay of 4 to 12 hours, severe metabolic acidosis
develops from accumulation of acid metabolites. Finally, delayed renal insufficiency follows deposition
of oxalate in renal tubules. Ethylene glycol toxicity is treated with 4-methylpyrazole (4-MP; fomepizole)
or ethanol to saturate the enzyme alcohol dehydrogenase and prevent conversion of ethylene glycol to its
toxic metabolites.

**Useful For:** Confirming and monitoring ethylene glycol toxicity

**Interpretation:** Toxic concentrations greater than or equal to 20 mg/dL may cause intoxication, central
nervous system (CNS) depression, metabolic acidosis, renal damage and hypocalcemia. Ingestion of
ethylene glycol can be fatal if patients do not receive immediate medical treatment.

**Reference Values:**
- Toxic concentration: > or =20 mg/dL

**Clinical References:**
CP: Drug addiction and drug abuse. In Goodman and Gilman's The Pharmacological Basis of
**Ethylene Oxide, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasms) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


**ETV6 (12p13.2) Rearrangement, FISH**

**Clinical Information:** Rearrangements involving 12p13 are some of the most commonly observed chromosomal abnormalities in hematologic malignancies. The ETV6 gene (ETS variant gene 6) codes for a transcription factor and is involved in deletions and translocations in both myeloid and lymphoid malignancies. Over 30 translocation partners have been identified.

**Useful For:** Providing diagnostic and prognostic information for patients with various lymphoid and myeloid malignancies.

**Interpretation:** A positive result is detected when the percent of cells with an abnormality exceeds
the normal cutoff for the probe set. A positive result suggests rearrangement of the ETV6 locus, which can be useful for diagnosis. A negative result suggests no rearrangement of the ETV6 gene region at 12p13.2.

Reference Values:
An interpretive report will be provided.

Clinical References:

ETV6F 63433

ETV6 (12p13.2) Rearrangement, FISH, Tissue

Clinical Information: ETV6 rearrangement is a recurrent abnormality in mammary analogue secretory carcinoma, secretory carcinoma of the breast, and infantile fibrosarcoma, but is not observed in tumors that share clinical and pathologic similarities.

Useful For: Providing diagnostic information and guiding treatment primarily for patients with mammary analogue secretory carcinoma, secretory carcinoma of the breast, and infantile fibrosarcoma

Interpretation: A positive result is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result suggests rearrangement of the ETV6 locus, which can be useful for diagnosis. A negative result suggests no rearrangement of the ETV6 gene region at 12p13.2.

Reference Values:
An interpretive report will be provided.

Clinical References:

EUCL 82758

Eucalyptus, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat
proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>4</td>
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<td>5</td>
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<tr>
<td>6</td>
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<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**FECLT**

**Euglobulin Clot Lysis Time**

**Reference Values:**

>60 min

**EMAY**

**Euroglyphus maynei, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**EHOR 82662 European Hornet, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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EVROL 35146

Everolimus, Blood

Clinical Information: Everolimus is an immunosuppressive agent derived from sirolimus (rapamycin). Both drugs function via inhibition of mTOR signaling, and share similar pharmacokinetic and toxicity profiles. Everolimus has a shorter half-life than sirolimus, which allows for more rapid achievement of steady-state pharmacokinetics. Everolimus is extensively metabolized, primarily by CYP3A4, thus its use with inducers or inhibitors of that enzyme may require dose adjustment. The most common adverse effects include hyperlipidemia, thrombocytopenia, and nephrotoxicity. Everolimus is useful as adjuvant therapy in renal cell carcinoma and other cancers. It recently gained FDA approval for prophylaxis of graft rejection in solid organ transplant, an application which has been accepted for years in Europe. The utility of therapeutic drug monitoring has not been established for everolimus as an oncology chemotherapy agent; however, measuring blood drug concentrations is common practice for its use in transplant. Therapeutic targets vary depending on the transplant site and institution protocol. Guidelines for heart and kidney transplants suggest that trough (immediately prior to the next scheduled dose) blood concentrations between 3 and 8 ng/mL provide optimal outcomes.

Useful For: Management of everolimus immunosuppression in solid organ transplant

Interpretation: Therapeutic targets vary by transplant site and institution protocol. Heart and kidney transplant guidelines suggest a therapeutic range of 3 to 8 ng/mL. Measurement of drug concentrations in oncology chemotherapy is less common, thus no therapeutic range is established for this application.

Reference Values:
3-8 ng/mL

Target steady-state trough concentrations vary depending on the type of transplant, concomitant immunosuppression, clinical/institutional protocols, and time post-transplant. Results should be interpreted in conjunction with this clinical information and any physical signs/symptoms of rejection/toxicity.


EWSF 35268

Ewing Sarcoma (EWS), 22q12 (EWSR1) Rearrangement, FISH, Tissue

Clinical Information: Ewing sarcoma (EWS)/primitive neuroectodermal tumors (PNET) are members of the small, round cell group of tumors that are thought to originate in cells of primitive
neuroectodermal origin with variable degrees of differentiation. The small, round cell group of tumors also includes rhabdomyosarcomas, desmoplastic small, round cell tumors, and poorly differentiated synovial sarcomas. Although immunohistochemical markers can be helpful in the correct diagnosis of these tumors, recent molecular studies have shown the specificity of molecular markers in differentiating specific subtypes of small, round blue-cell tumors. Accurate diagnosis of each tumor type is important for appropriate clinical management of patients. Ewing tumors are characterized cytogenetically by rearrangements of the EWSR1 gene at 22q12 with FLI1 at 11q24 (t(11;22)) or ERG at 21q22 (t(21;22)) in 85% and 5% to 10% of Ewing tumors, respectively. Less than 1% of cases may have other fusion partners such as ETV1 at 7p22, E1AF at 17q12, or FEV at 2q33. Detection of these transcripts by reverse transcriptase-PCR (RT-PCR) (EWS, Ewing Sarcoma RT-PCR) that allows specific identification of the t(11;22) and the t(21;22), has greatly facilitated the diagnosis of Ewing tumors. However, if the quality of the available RNA is poor, the results are equivocal, or if a rare translocation partner is present, FISH testing has proven to be useful in identifying the 22q12 EWS gene rearrangement in these tumors.

**Useful For:** Supporting the diagnosis of Ewing sarcoma (EWS)/primitive neuroectodermal tumor (PNET), myxoid chondrosarcoma, desmoplastic small, round cell tumor, clear cell sarcoma, and myxoid liposarcoma when used in conjunction with an anatomic pathology consultation. An aid in the diagnosis of EWS when reverse transcriptase-PCR results are equivocal or do not support the clinical picture.

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the EWSR1 FISH probe set. A positive result is consistent with a diagnosis of Ewing sarcoma (EWS)/primitive neuroectodermal tumors (PNET). A negative result suggests that an EWSR1 rearrangement is not present but does not exclude the diagnosis of EWS/PNET.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Ewing Sarcoma, by Reverse Transcriptase PCR (RT-PCR)**

**Clinical Information:** Ewing sarcoma (ES) and primitive neuroectodermal tumor (PNET), a closely related tumor, are members of the small round-cell tumor group that also includes rhabdomyosarcoma, synovial sarcoma, lymphoma, Wilms tumor, and desmoplastic small round-cell tumor. ES is the second most common malignant tumor of bone in children and young adults. It is an aggressive osteolytic tumor with a high risk of metastasizing. ES can also present as a soft tissue tumor mass. These tumors are usually bland and undifferentiated with relatively low mitotic indexes, which is misleading in light of the rapid growth commonly observed clinically. While treatment and prognosis depend on establishing the correct diagnosis, the diagnosis of sarcomas that form the small round-cell tumor group can be very difficult by light microscopic examination alone, especially true when only small-needle biopsy specimens are available for examination. The use of histochemical and immunohistochemical stains (eg, MIC2 [CD99], desmin, myogenin, myoD1, WT1) can assist in establishing the correct diagnosis, but these markers are not entirely specific for ES/PNET. Expertise in soft tissue and bone pathology are often needed. Studies have shown that some sarcomas have specific recurrent chromosomal translocations. These translocations produce highly specific gene fusions that help define and characterize subtypes of sarcomas that are useful in the diagnosis of these lesions.(1-4) The balanced t(11;22)(q24;q12) chromosomal translocation produces the EWSR1-FLI1 fusion transcript and is present in 95% of ES and PNET. Because the EWSR1-FLI1 fusion transcript is a common finding in ES/PNET, in soft tissues these 2 lesions are essentially identical. Less common are the t(21;22)(p22;q12) or EWSR1-ERG transcript, present in <5% of ES/PNET tumors, and the t(7;22)(p22;q12) or EWSR1-FEV transcript, present in <1% of these tumors. These fusion transcripts can be detected by reverse-transcriptase PCR (RT-PCR), by
FISH, chromogenic in situ hybridization, or by classical cytogenetic analyses. The RT-PCR and FISH procedures are the most sensitive methods to detect these fusion transcripts.(3)

**Useful For:** Supporting a diagnosis of Ewing sarcoma and primitive neuroectodermal tumors

**Interpretation:** A positive EWSR1-FLI1 or EWSR1-ERG result is consistent with a diagnosis of Ewing sarcoma and primitive neuroectodermal tumor (ES/PNET). Sarcomas other than ES/PNET, and carcinomas, melanomas, and lymphomas are negative for the fusion products. A negative result does not rule out a diagnosis of ES/PNET.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

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**F-Actin Ab, IgG, S**

**Clinical Information:** Autoimmune hepatitis (AIH) is caused by chronic inflammation within the liver, resulting in damage to the hepatocytes.(1) Initially, patients with AIH may be clinically asymptomatic, usually identified only through an incidental finding of abnormal liver function tests. At a more advanced stage, patients may manifest with symptoms such as jaundice, pruritus, and/or ascites, which are secondary to the more extensive liver damage. As implied by the name, AIH has many characteristics of an autoimmune disease, including female predominance, hypergammaglobulinemia, association with specific HLA alleles, responsiveness to immunosuppression, and the presence of autoantibodies. There are several autoantibodies associated with AIH, although the most common is anti-smooth muscle antibody (anti-SMA). Anti-SMAs are generally identified by indirect immunofluorescence using a smooth muscle substrate. The antigen specificity of anti-SMAs in the context of AIH has been identified as filamentous-actin (F-actin).(2) Because the clinical symptoms of AIH are nonspecific, being found in a variety of liver diseases (drug/alcohol-associated hepatitis, viral hepatitis, primary sclerosing cholangitis, etc), the diagnosis can be challenging. A set of diagnostic criteria for AIH has been published, and includes the presence of various autoantibodies, elevated total IgG, evidence of hepatitis on liver histology, and absence of viral markers.(3) The combination of autoantibody serology, specifically anti-SMAs and anti-F-Actin antibodies with liver histology and thorough clinical evaluation are useful in the evaluation of patients with suspected autoimmune hepatitis.

**Useful For:** Evaluating patients suspected of having autoimmune hepatitis

**Interpretation:** Seropositivity for anti-F-Actin antibodies is consistent with a diagnosis of autoimmune hepatitis (AIH). A negative result for anti-F-Actin antibodies does not exclude a diagnosis of AIH. In a study conducted at Mayo Clinic, the F-Actin ELISA had a clinical sensitivity of 92.9% when using the manufacturer’s recommended cutoff of 20.0 U. In addition, the F-Actin ELISA had a clinical specificity of 76.7% when using the aforementioned cutoffs. See Supportive Data.

**Reference Values:**
Negative: <20.0 U
Weak Positive: 20.0-30.0 U
Positive: >30.0 U

**Clinical References:**
1. Invernizzi P, Lleo A, Podda M: Interpreting serological tests in diagnosing...

F2-Isoprostanes, Urine

**Clinical Information:** Oxidative stress results from the generation and overaccumulation of reactive oxygen and nitrogen species and has been shown to damage lipoproteins, lipids, DNA, and proteins. Furthermore, oxidative stress may modulate modifications to these lipoproteins and DNA such that endothelial function and inflammatory processes are altered, ultimately resulting in the initiation and progression of atherosclerosis and cardiovascular disease (CVD). Isoprostanes are a series of prostaglandin-like compounds produced via the free-radical catalyzed peroxidation of arachidonic acid, independent of the cyclooxygenase-derived prostaglandins. F2-isoprostanes are considered the "gold standard" test for quantifying lipid peroxidation/oxidative stress in vivo. 15-F2t-isoprostane (15-F2t-IsoP), also referred to as 8-iso-PGF2 alpha or 8-isoprostane F2 alpha, is 1 of the F2-isoprostanes produced in abundance in vivo and has demonstrated potency as a vasoconstrictor within the vasculature of the heart, brain, lung, and kidneys. Generation of 15-F2t-IsoP induces downstream effects including proliferation of vascular smooth muscle cells and release of endothelin. Additional evidence suggests that F2-isoprostanes may increase aspirin resistance to platelet aggregation within platelets and whole blood. F2-isoprostanes are advantageous over other markers of lipid peroxidation due to their in vivo and in vitro stability and are detectable in a variety of human tissues and biological fluids including plasma, urine, lavage fluid, RBCs, and cerebrospinal fluid. Quantitation of F2-isoprostanes in a random urine specimen is considered to be the most accurate and robust measurement of circulating isoprostanes and is a noninvasive method of assessment.

**Useful For:** The assessment of in vivo lipid peroxidation and considered to be an index of systemic oxidative stress over time

**Interpretation:** Elevated urinary F2-isoprostanes reflect widespread oxidative stress and systemic burden of lipid peroxidation end products. Quantitation of F2-isoprostanes in urine is highly dependent upon the methodology utilized; however, mass spectrometry methods (gas chromatography-mass spectrometry or liquid chromatography-tandem mass spectrometry) assays yield superior sensitivity and analytical specificity compared with immunoassays. F2-isoprostanes demonstrate superior clinical sensitivity compared to other oxidative stress biomarkers but lack clinical specificity for any particular disease. Pharmacological treatment with antioxidant supplementation, hypoglycemic agents in diabetes, smoking cessation, and weight reduction have all been shown to decrease production of F2-isoprostanes.

**Reference Values:**
> 18 years: ≤ 1.0 ng/mg creatinine
< 18 years: not established


Fabry Disease, Full Gene Analysis

**Clinical Information:** Fabry disease is an X-linked recessive disorder with an incidence of approximately 1 in 50,000 males. Symptoms result from a deficiency of the enzyme alpha-galactosidase A (alpha-Gal A). Reduced alpha-Gal A activity results in accumulation of glycosphingolipids in the lysosomes of both peripheral and visceral tissues. Severity and onset of symptoms are dependent on the
residual alpha-Gal A activity. Males with <1% alpha-Gal A activity have the classic form of Fabry disease. Symptoms can appear in childhood or adolescence and usually include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, and corneal opacity. By middle age, most patients develop renal insufficiency leading to end-stage renal disease, as well as cardiac and cerebrovascular disease. Males with >1% alpha-Gal A activity may present with a variant form of Fabry disease. The renal variant generally has onset of symptoms in the third decade. The most prominent feature in this form is renal insufficiency and, ultimately, end-stage renal disease. Individuals with the renal variant may or may not have other symptoms of classic Fabry disease. Individuals with the cardiac variant are often asymptomatic until they present with cardiac findings such as cardiomyopathy or mitral insufficiency later in life. The cardiac variant is not associated with renal failure. Female carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severe. Measurement of alpha-Gal A activity is not generally useful for identifying carriers of Fabry disease, as many of these individuals have normal levels of alpha-Gal A. Mutations in the GLA gene result in deficiency of alpha-Gal A. Most of the mutations identified to date are family specific. Full sequencing of the GLA gene identifies over 98% of the sequence variants in the coding region and splice junctions. In addition, our assay detects the intron 4 mutation common in the Taiwanese population.(1) The following algorithms are available in Special Instructions: -Fabry Disease: Newborn Screen-Positive Follow-up algorithm -Fabry Disease Testing Algorithm

Useful For: Confirmation of a diagnosis of classic or variant Fabry disease in affected males with reduced alpha-Gal A enzyme activity Carrier or diagnostic testing for asymptomatic or symptomatic females, respectively

Interpretation: All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics (AMCG) recommendations.(2) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


**Factor 13a (FAC13A) Immunostain, Technical Component Only**

**Clinical Information:** Factor XIIIa, a blood and intracellularly produced coagulation factor, has been found in a variety of cell types, including fibroblast-like mesenchymal cells, and has been shown to stimulate the proliferation of fibroblasts and neoplastic cells in vitro. Immunohistochemical staining for factor XIIIa labels normal dermal dendrocytes, the large stellate fibroblasts found in acquired digital fibrokeratomas, angiofibromas, and oral fibroma, and a proportion of cells in histiocytomas. Factor XIIIa immunostain also produces cytoplasmic staining of dermal dendrocytes in normal skin and of a proportion of cells in histiocytomas.

**Useful For:** Aids in the identification of acquired digital fibrokeratomas, angiofibromas, and oral fibroma, and a proportion of cells in histiocytomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation.
and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Factor 8 Related Antigen (FAC8) Immunostain, Technical Component Only**

**Clinical Information:** Factor 8 shows diffuse cytoplasmic staining of endothelial cells, megakaryocytes, and platelets; and can be used to support endothelial cell lineage in angiosarcomas.

**Useful For:** Marker of endothelial cell lineage

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Factor II Inhibitor Screen**

**Reference Values:** Negative

**Factor IX Inhibitor Evaluation**

**Clinical Information:** Factor IX inhibitors arise in patients with severe hemophilia B after factor IX transfusion. Patients with factor IX inhibitors may also develop anaphylactic reactions in response to factor IX infusions. Acquired factor IX inhibitors, occurring in previously healthy people, are exceedingly rare.

**Useful For:** Detection and titering of coagulation inhibitor to the specific factor requested, primarily factor IX in patients with hemophilia B This test is not useful for detecting presence of inhibitors directed
against other clotting factors and is not useful for the detection of a nonspecific circulating anticoagulant. This test is not useful for the detection of lupus anticoagulants.

**Interpretation:** Normally, there is no inhibitor (i.e., negative result). If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

**Reference Values:**

**FACTOR IX ACTIVITY ASSAY**
- **Adults:** 65-140%
  - Normal, full-term newborn infants or healthy premature infants may have decreased levels (> or =20%), which may not reach adult levels for > or =180 days postnatal.*
  - *See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

**FACTOR IX INHIBITOR SCREEN**
- **Negative**

**BETHESDA TITER**
- **0 Units**

**Clinical References:**

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**Factor IX Inhibitor Screen**
**Reference Values:**
- **Negative**

**Factor IX Known Mutation Sequencing**
**Reference Values:**
- Only orderable as a reflex at order entry for unit code FIXKM / Hemophilia B, Factor IX Gene Known Mutation Screening (Carrier Detection).

**Factor IX Mut Scrn Gene Sequencing**
**Reference Values:**
- Only orderable as a reflex at order entry for test FIXMS / Hemophilia B, Factor IX Gene Mutation Screening.

**Factor V Inhibitor Screen**
**Reference Values:**
- **Negative**

**Factor V Leiden (R506Q) Mutation, Blood**
**Clinical Information:** Venous thromboembolism includes deep vein thrombosis and its complication, pulmonary embolism. Plasma from 12% to 20% of venous thromboembolism patients is resistant to the anticoagulant effect of activated protein C (APC resistance). Essentially all patients with hereditary APC resistance have a single nucleotide mutation of the coagulation factor V gene (F5
rs6025), which encodes for an arginine (R) to glutamine (Q) substitution at position 506 of the factor V protein (FV R506Q). The factor V Leiden (R506Q) gene mutation test is a direct mutation analysis of patient blood leukocyte genomic DNA. We recommend the coagulation-based activated protein C (APC)-resistance ratio (mixing with factor V-deficient plasma) as the initial screening assay for APC-resistance. Depending on the assay system, the APC-resistance ratio may be indeterminate for patients with a lupus anticoagulant or extremely high heparin levels.

**Useful For:** Factor V Leiden mutation testing should be reserved for patients with clinically suspected thrombophilia and: 1) APC-resistance proven or suspected by a low or borderline APC-resistance ratio, or 2) a family history of factor V Leiden.

**Interpretation:** The interpretive report will include specimen information, assay information, background information, and conclusions based on the test results (normal, heterozygous FV R506Q, homozygous FV R506Q).

**Reference Values:**

**Negative**


### F7_IS
 **Factor VII Inhibitor Screen**

**Reference Values:**

Negative

**Clinical Information:**

FACTOR VII ACTIVITY ASSAY

Adults: 55-200%

Normal, full-term newborn infants or healthy premature infants usually have normal or elevated factor VIII.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

FACTOR VII INHIBITOR SCREEN

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**F8INH**
 **Factor VIII Inhibitor Evaluation**

**Clinical Information:** Factor VIII inhibitors are IgG antibodies directed against coagulation FVIII that typically result in development of potentially life-threatening hemorrhage. These antibodies may develop in 1 of 4 different patient populations: -Patients with congenital FVIII deficiency (hemophilia A) in response to therapeutic infusions of factor VIII concentrate -Elderly nonhemophilic patients (not previously factor VIII deficient) -Women in postpartum period -Patients with other autoimmune illnesses

**Useful For:** Detecting the presence and titer of a specific factor inhibitor directed against coagulation factor VIII. This test is not useful for detecting the presence of inhibitors directed against other clotting factors and will not detect the presence of lupus anticoagulants.

**Interpretation:** Normally, there is no inhibitor, (ie, negative result). If the screening assays indicate the presence of an inhibitor, it will be quantitated and reported in Bethesda (or equivalent) units.

**Reference Values:**

FACTOR VIII ACTIVITY ASSAY

Adults: 55-200%

Normal, full-term newborn infants or healthy premature infants usually have normal or elevated factor VIII.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

### 10_IS 7812 Factor X Inhibitor Screen
**Reference Values:**
Negative

### 11_IS 7804 Factor XI Inhibitor Screen
**Reference Values:**
Negative

### FF13F 57811 Factor XIII, Functional
**Reference Values:**
57 â€“ 192 % activity

### FX13M 57302 Factor XIII, Qualitative, with Reflex to Factor XIII 1:1 Mix
**Reference Values:**
Factor XIII, Qualitative: No Lysis
Factor XIII, 1:1 Mix: Not Applicable

### FOGT 82379 False Oat Grass, IgE
**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


**False Ragweed, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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6 > or =100  Strongly positive Reference values apply to all ages.


FDP 35419

Familial Dysautonomia, Mutation Analysis, IVS20(+6T->C) and R696P

Clinical Information: Familial dysautonomia affects sensory, parasympathetic, and sympathetic neurons. Patients experience gastrointestinal dysfunction, pneumonia, vomiting episodes, altered sensitivity to pain and temperature, and cardiovascular problems. Progressive neuronal degeneration continues throughout the lifespan. Mutations in the inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein gene (IKBKAP) cause the clinical manifestations of familial dysautonomia. The carrier rate in the Ashkenazi Jewish population is 1 in 31. There are 2 common mutations in the Ashkenazi Jewish population: IVS20(+6)T->C and R696P. The carrier detection rate for these 2 mutations is 99%.

Useful For: Carrier screening for familial dysautonomia in individuals of Ashkenazi Jewish ancestry Prenatal diagnosis of familial dysautonomia in at-risk pregnancies Confirmation of a clinical diagnosis of familial dysautonomia in individuals of Ashkenazi Jewish ancestry

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.


FHRGP 65748

Familial Hypercholesterolemia and Related Disorders Multi-Gene Panel

Clinical Information: Familial hypercholesterolemia (FH) is an inherited condition that results in elevated levels of low-density lipoprotein cholesterol (LDL-C). FH is associated with premature cardiovascular disease and myocardial infarction. Early diagnosis and treatment help to mitigate these risks. The most common form of FH is autosomal dominant heterozygous familial hypercholesterolemia (heFH) caused by loss-of-function variants found in the LDLR gene. Recent studies suggest that the prevalence of heFH is as high as 1 in 200 to 250, and may be even higher in some founder populations such as those of French Canadian, Ashkenazi Jewish, Lebanese, and South African descent. In general, FH heterozygotes have 2-fold elevations in plasma cholesterol and develop coronary atherosclerosis after the age of 30. Hundreds of variants have been identified in the LDLR gene. The majority of variants in the LDLR gene are small point variants (missense, nonsense) or small insertions or deletions. Most of these variants are detectable by sequencing of the LDLR gene. An additional 10% of variants in the LDLR gene are large intragenic rearrangements, such as large exon deletions and duplications. Absent or decreased LDL-receptor results in a reduced capacity to clear LDL from circulation. A more severe form of familial hypercholesterolemia can also be caused by homozygous or compound heterozygous (biallelic) variants in the LDLR gene. This condition is referred to as homozygous familial hypercholesterolemia (hoFH). Recent studies suggest the prevalence of hoFH is as high as 1 in 250,000. Individuals with homozygous FH typically have severe hypercholesterolemia (generally >650...
mg/dL) with the presence of cutaneous xanthomas prior to 4 years of age, childhood coronary heart disease, and oftentimes, death from myocardial infarction prior to 20 years of age. Another form of autosomal dominant hypercholesterolemia is called familial defective apolipoprotein B-100 (FDB). FDB is caused by loss-of-function variants in the APOB gene that reduce the binding affinity between the protein encoded by APOB (apolipoprotein B-100) and the protein encoded by LDLR (low-density lipoprotein receptor). Individuals with heterozygous APOB variants have elevated LDL-C, although the elevation is typically less than that observed in individuals with heterozygous LDLR variants; increased rates of coronary artery calcifications; and premature myocardial infarction. Approximately 1 in 1667 Northern European Caucasians carry the R3500Q (HGVS: c.10580G->A, p.Arg3527Gln) variant in the APOB gene, and approximately 1 in 800 East Asians carry the R3500W (HGVS: c.10579C->T, p.Arg3527Trp) variant in the APOB gene. Although other variants resulting in autosomal dominant hypercholesterolemia have been described in APOB; most appear within a hotspot (or frequently affected) region surrounding the p.Arg3527 residue. Homozygosity and compound heterozygosity for APOB variants can also occur; these individuals typically have LDL-C levels above 300 mg/dL. Individuals with homozygous FDB are sometimes misdiagnosed with heFH. Autosomal dominant hypercholesterolemia can also be caused by gain-of-function variants in the PCSK9 gene. Variants in this gene are rare, but when present, they result in increased PCSK9 protein levels, leading to increased degradation of low-density lipoprotein receptors. Recently, drugs targeting PCSK9 (called PCSK9 inhibitors) have been developed. These drugs inhibit the binding of PCSK9 to LDL-receptors, thus reducing degradation of LDL-receptors and increasing the amount of LDL-C cleared in certain individuals. Loss-of-function variants in the LDLRAP1 gene cause a rare form of familial hypercholesterolemia called autosomal recessive familial hypercholesterolemia. Once LDL-C binds to the LDL-receptor the LDLRAP1 protein binds to the complex and internalization of the complex, which results in degradation of either the LDL particle or the entire complex occurs. Unlike autosomal dominant hypercholesterolemia caused by heterozygous variants in LDLR, APOB, and PCSK9, biallelic variants in LDLRAP1 are required for elevated LDL-C levels. Individuals with homozygous or compound heterozygous LDLRAP1 variants typically have LDL-C levels above 400 mg/dL, cutaneous and tendon xanthomas, and coronary artery disease. Homozygosity for LDLRAP1 variants does not result in elevated cholesterol levels, so the parents of children with biallelic LDLRAP1 variants are typically normocholesterolemic. Sitosterolemia, a rare autosomal recessive inherited lipid metabolism disease, is caused by biallelic variants in the ABCG5 or ABCG8 genes and has similar clinical manifestations to familial hypercholesterolemia. Sitosterolemia is characterized by increased intestinal absorption of plant sterols (15% to 60% compared to <5% in unaffected individuals). These individuals also typically have elevated total cholesterol and LDL cholesterol levels, although individuals with normal LDL-C levels have also been reported. Untreated individuals with sitosterolemia exhibit tendon and tuberous xanthomas, and coronary artery disease. Homozygosity for LDLRAP1 variants does not result in elevated cholesterol levels, so the parents of children with biallelic LDLRAP1 variants are typically normocholesterolemic. 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Identification of the genetic cause of an individual’s clinical features helps to determine the appropriate treatment for their clinical features. Treatment is aimed at lowering plasma LDL levels and plasma sterol levels. Common treatments included statins, LDL apheresis, dietary modifications, and more recently PCSK9 inhibitors. Screening of at-risk family members allows for effective primary prevention by instituting appropriate therapy and dietary modifications at an early stage. Table1. Genes included in the Familial Hypercholesterolemia and Related Disorders Multi-Gene Panel Gene Symbol (alias) Protein OMIM Inheritance Phenotype Disorder ABCG5 ATP-binding cassette, subfamily G, member 5 605459 AR Sitosterolemia ABCG8 ATP- binding cassette, subfamily G, member 8 605460 AR Sitosterolemia APOB Apolipoprotein B 107730 AD AR Hypercholesterolemia, due to ligand-defective apo B Hypobetalipoproteinemia LDLR Low density lipoprotein receptor 606945 AD Hypercholesterolemia, familial LDLRAP1 Low density lipoprotein receptor adaptor protein 1 605747 AR Hypercholesterolemia, familial, autosomal recessive PCSK9 Proprotein convertase, subtilisin/kexin-type, 9 607786 AD Hypercholesterolemia, familial, 3 AD: autosomal dominant AR: autosomal recessive

**Useful For:** Confirming a clinical diagnosis of familial hypercholesterolemia or sitosterolemia Cascade screening of at-risk family members and early diagnosis, treatment, and dietary modifications

Ascertaining carrier status of family members of individuals diagnosed with familial hypercholesterolemia for genetic counseling purposes
**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**FMTT 63032**

**Familial Mutation, Targeted Testing**

**Clinical Information:** This test is available to test for the presence of 1 or more mutations previously identified in a family member. Targeted testing is used for diagnostic or predictive testing in cases in which mutations have been previously identified in an affected family member. Targeted testing is available for a specific subset of genes only. Genes Available for Testing* ABCD1 ACADM ACADS ACADVL AGXT APC APOA1 APOA2 ARSA ARSB ATP7B AXIN2 BMPR1A BRC2 BTD CASR CDH1 CDKN1C CFTR CHEK2 CPOX CPT2 CTRC DMD FCHI FGA FLCN FTCD GAA GALC GALT GBA GLA GNPTAB GNS GRHPR GRN HEXA HGSNAT HMBS IDS IDUA LYZ MAPT MAX MECP2 MEFV MLH1 MLH3 MLYCD MMACHC MMADHC MSH2 MSH6 MUTYH NAGLU NPC1 NPC2 PHH1 PMS2 PPOX PRSS1 PSAP PTEN RA11 RET SERPINA1 SGC5 SDHAF2 SDHB SDHC SDHD SEPT9 SGSH SLC25A20 SMAD4 SMN1 SMPD1 SPINK1 STK11 SUMF1 TACSTD1/EPACAM TMEM127 TNFRSF1A TP53 TTR UBE3A VHL.

FMTT is available for family members of a patient who had testing performed by the molecular genetics laboratory at Mayo Medical Laboratories. For these individuals, FMTT can be used to detect variants in the genes listed in the table above, in addition to any gene (excluding pharmacogenomics variants) via large panels. Contact the laboratory to determine whether adequate DNA is available in the laboratory or if a new proband sample is required. Refer to the following resources for information regarding the listed gene targets. GeneReviews-NCBI Bookshelf, available at www.ncbi.nlm.nih.gov/books/NBK1116/ or OMIM, available at www.omim.org/. Testing may be delayed if the required documentation is not received (ie, patient information sheet).

**Useful For:** Diagnostic or predictive testing for specific conditions when 1 or more mutations have been identified in a family member Carrier screening for individuals at risk for having a mutation that was previously identified in a family member.
**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.


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### Fanconi Anemia C Mutation Analysis, IVS4(+4)A->T and 322delG

**Clinical Information:** Fanconi anemia is an aplastic anemia that leads to bone marrow failure and myelodysplasia or acute myelogenous leukemia. Physical findings include short stature; upper limb, lower limb, and skeletal malformations; and abnormalities of the eyes and genitourinary tract. The proteins encoded by the genes associated with Fanconi anemia may work together to repair DNA damage. Mutations in several genes have been associated with Fanconi anemia, although 1 mutation, IVS4(+4)A->T in the FANCC gene has been shown to be common in the Ashkenazi Jewish population. The carrier rate in the Ashkenazi Jewish population is 1 in 89 and the detection rate for this mutation using this assay is greater than 99%. A second FANCC mutation, 322delG, is overrepresented in patients of Northern European ancestry.

**Useful For:** Carrier screening for Fanconi anemia in individuals of Ashkenazi Jewish ancestry Prenatal diagnosis of Fanconi anemia in at-risk pregnancies Confirmation of suspected clinical diagnosis of Fanconi anemia in individuals of Ashkenazi Jewish ancestry

**Interpretation:** An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided.


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### Fascin Immunostain, Technical Component Only

**Clinical Information:** Fascin is an actin-bundling protein that is present in antigen-presenting cells, and upregulated in Epstein Barr virus-positive lymphocytes and Hodgkin cells. Antibodies to fascin result in distinct cytoplasmic staining of the Langerhans cells, follicular dendritic cells, and interdigitating reticulum cells in normal lymph nodes. Fascin is usually positive in classical Hodgkin lymphoma and negative in lymphocyte predominant Hodgkin lymphoma.

**Useful For:** Classification of lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in...
the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**Fat, Feces**

**Clinical Information:** Total fecal lipids include glycerides, phospholipids, glycolipids, soaps, sterols, cholesteryl esters, and sphingolipids. Excess fecal fat in stool, (steatorrhea) is indicative of malabsorption disorders, such as pancreatic insufficiency or Whipple disease. Therefore, measurement of the fecal fats can be useful in establishing a diagnosis of such pancreatic diseases as cystic fibrosis, chronic pancreatitis, neoplasia, or stone obstruction, and such intestinal diseases as Whipple disease, regional enteritis, tuberculous enteritis, gluten-induced enteropathy (also called celiac disease or sprue), and the atrophy of malnutrition. Distinguishing free fatty acids from neutral fats, once thought to be helpful in the differential diagnosis of pancreatic disease, has fallen out of favor. Note that the composition of fats in the stool, normally predominately free fatty acids, can change significantly to predominately neutral fatty acids when the patient is on orlistat. This test does not distinguish between free and neutral fatty acids.

**Useful For:** Diagnosing fat malabsorption due to pancreatic or intestinal disorders Monitoring effectiveness of enzyme supplementation in certain malabsorption disorders

**Interpretation:** Excretion of more than 7 grams fat/24 hours, when on a diet of 100 to 150 g of fat, is suggestive of a malabsorption defect. Abnormal results from a random specimen should be confirmed by submission of a timed collection. Test values for timed fecal fat collections will be reported in terms of grams fat collected; the duration of the collection may be 24, 48, 72, or 96 hours. Test values for random fecal fat collections will be reported in terms of percent fat. Coefficient of Fat Absorption (CFA) can be calculated as follows: (grams fat consumed â€“ grams of fat excreted) x 100 CFA = -------------------------------------------------------- grams of fat consumed

**Reference Values:**

**TIMED COLLECTION**

> or =18 years: 2-7 g fat/24 hours

Reference values have not been established for patients who are <18 years of age.

**RANDOM COLLECTION**

All ages: 0-19% fat


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**Fatty Acid Oxidation Probe Assay, Fibroblast Culture**

**Clinical Information:** Mitochondrial fatty acid beta-oxidation plays an important role in energy production, particularly in skeletal and heart muscle, and in hepatic ketone body formation. Disorders of fatty acid oxidation (FAO) are characterized by hypoglycemia, hepatic dysfunction, encephalopathy, skeletal myopathy, and cardiomyopathy. Most FAO disorders have a similar presentation and their biochemical diagnosis can, at times, be difficult. Commonly used metabolite screens such as urine organic acids, plasma acylcarnitines, and fatty acids are influenced by dietary factors and the clinical
status of the patient. This often leads to incomplete diagnostic information or even false-negative results. Enzyme assays are limited to 1 enzyme per assay, and molecular assays for common mutations are limited by the frequent occurrence of compound heterozygous patients with uncommon, private mutations that must be distinguished from unaffected carriers. Furthermore, neither specific enzyme assays nor molecular genetic testing is available for all of the known defects. The purpose of the in vitro probe assay is to offer screening for several defects of FAO and organic acid metabolism under controlled laboratory conditions using fibroblast cultures.

Useful For: In vitro confirmation of biochemical diagnoses of the following fatty acid oxidation disorders: -Short-chain acyl-CoA dehydrogenase (SCAD) deficiency -Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency -Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency -Trifunctional protein deficiency -Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency -Carnitine palmityl transferase deficiency type II (CPT-II) -Carnitine-acylcarnitine translocase (CACT) deficiency In addition, the following organic acid disorders can be confirmed by this assay: -2-Methylbutyryl-CoA dehydrogenase (SBCAD) deficiency -Isobutyryl-CoA dehydrogenase (IBD) deficiency

Interpretation: Abnormal results will include a description of the abnormal profile, in comparison to normal and abnormal control controls. In addition, the concentration of those acylcarnitine species that abnormally accumulated in the cell medium are provided and compared to the continuously updated reference range based on analysis of normal controls. Interpretations of abnormal acylcarnitine profiles also include information about the results' significance, a correlation to available clinical information, possible differential diagnoses, recommendations for additional biochemical testing and confirmatory studies if indicated, name and phone number of contacts who may provide these studies at the Mayo Clinic or elsewhere, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values: An interpretive report will be provided.


Fatty Acid Profile, Comprehensive (C8-C26), Plasma

Clinical Information: Fatty Acid Deficiency/Excess: Fats are important sources of energy for tissues and for the function and integrity of cellular membranes. Deficiencies are commonly caused by inadequate dietary intake of lipids due to an unbalanced diet, long-term parenteral nutrition, or by intestinal malabsorption. Linoleic acid, an omega-6 fatty acid, and alpha-linolenic acid, an omega-3 fatty acid, are considered essential fatty acids in that they cannot be made by the body and are essential components of the diet. The major clinical manifestations associated with essential fatty acid deficiency (EFAD) include dermatitis, increased water permeability of the skin, increased susceptibility to infection, and impaired wound healing. Biochemical abnormalities may be detected before the onset of recognizable clinical manifestations. EFAD can be detected by diminished levels of the essential fatty acids linoleic acid and alpha-linolenic acid, as well as by increases in the triene:tetraene ratio. Excess dietary fatty acids have been linked to the onset of cardiovascular disease. Elevated levels of linoleic acid can contribute to overproduction of the proinflammatory 2-series local hormones. Fatty Acid Oxidation (FAO) Disorders: Mitochondrial beta-oxidation is the main source of energy to skeletal and heart muscle during periods of fasting. When the body's supply of glucose is depleted, fatty acids are mobilized from adipose tissue and...
converted to ketone bodies thorough a series of steps providing an alternate source of energy. Deficient enzymes at any step in this pathway prevent the production of energy during periods of physiologic stress such as fasting or intercurrent illness. The major clinical manifestations associated with FAO disorders include hypoketotic hypoglycemia, liver disease and failure, skeletal myopathy, dilated/hypertrophic cardiomyopathy, and sudden unexpected death in early life. Signs and symptoms may vary greatly in severity, combination, and age of presentation. Life-threatening episodes of metabolic decompensation frequently occur after periods of inadequate calorie intake or intercurrent illness. When properly diagnosed, patients with FAO disorders respond favorably to fasting avoidance, diet therapy, and aggressive treatment of intercurrent illnesses, with significant reduction of morbidity and mortality. Disease-specific characteristic patterns of metabolites from FAO disorders are detectable in blood, bile, urine, and cultured fibroblasts of living and many deceased individuals. Quantitative determination of C8-C18 fatty acids is an important element of the workup and differential diagnosis of candidate patients. Fatty acid profiling can detect quantitatively modest, but nevertheless significant, abnormalities even when patients are asymptomatic and under dietary treatment. Enzyme and molecular confirmatory testing is also available for many of the FAO disorders at Mayo Medical Laboratories. Peroxisomal Disorders: Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include disorders of peroxisomal biogenesis with defective assembly of the entire organelle and single peroxisomal enzyme/transporter defects where the organelle is intact but a specific function is disrupted. Peroxisomal beta-oxidation of VLCFA is impaired in all disorders of peroxisomal biogenesis and in selected single enzyme deficiencies, particularly X-linked adrenoleukodystrophy, resulting in elevated concentrations of VLCFA in serum or plasma. POXP / Fatty Acid Profile, Peroxisomal (C22-C26), Plasma or POX / Fatty Acid Profile, Peroxisomal (C22-C26), Serum is the preferred screening test for evaluating patients with possible peroxisomal disorders, single-enzyme defects of peroxisomal metabolism such as X-linked adrenoleukodystrophy, or peroxisomal biogenesis disorders (Zellweger syndrome spectrum). Confirmatory testing for X-linked adrenoleukodystrophy (XALDZ / X-Linked Adrenoleukodystrophy, Full Gene Analysis) via molecular genetic analysis is available at Mayo Medical Laboratories.

Useful For: This plasma test is a comprehensive profile that provides information regarding mitochondrial and peroxisomal fatty acid metabolism, and the patient’s nutritional status Monitoring patients undergoing diet therapy for mitochondrial or peroxisomal disorders (possibly inducing essential fatty acid deficiency in response to restricted fat intake) Monitoring treatment of essential fatty acid deficiency Monitoring the response to provocative tests (fasting tests, loading tests)

Interpretation: An increased triene:tetraene ratio is consistent with essential fatty acid deficiency. Fatty acid oxidation disorders are recognized on the basis of disease-specific patterns that are correlated to the results of other investigations in plasma (carnitine, acylcarnitines) and urine (organic acids, acylglycines). Increased concentrations of very long-chain fatty acids (VLCFA) C24:0 and C26:0 are seen in peroxisomal disorders, X-linked adrenoleukodystrophy, adrenomyeloneuropathy, and Zellweger syndrome (cerebrohepatorenal syndrome). Increased concentrations of phytic acid (along with normal pristanic acid concentrations) are seen in the Refsum disease (phytanase deficiency). Phytanic acid concentration also may be increased in other peroxisomal disorders and, when combined with the VLCFA, pristanoic acid, and pipecolic acid, allows differential diagnosis of peroxisomal disorders.

Reference Values:

Octanoic Acid, C8:0
<1 year: 7-63 nmol/mL
1-17 years: 9-41 nmol/mL
> or =18 years: 8-47 nmol/mL

Decenoic Acid, C10:1
<1 year: 0.8-4.8 nmol/mL
1-17 years: 1.6-6.6 nmol/mL
> or =18 years: 1.8-5.0 nmol/mL

Decanoic Acid, C10:0
<1 year: 2-62 nmol/mL
1-17 years: 3-25 nmol/mL

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  Page 869
Laurolec Acid, C12:1
<1 year: 0.6-4.8 nmol/mL
1-17 years: 1.3-5.8 nmol/mL
> or =18 years: 1.4-6.6 nmol/mL

Lauric Acid, C12:0
<1 year: 6-190 nmol/mL
1-17 years: 5-80 nmol/mL
> or =18 years: 6-90 nmol/mL

Tetradecadienoic Acid, C14:2
<1 year: 0.3-6.5 nmol/mL
1-17 years: 0.2-5.8 nmol/mL
> or =18 years: 0.8-5.0 nmol/mL

Myristoleic Acid, C14:1
<1 year: 1-46 nmol/mL
1-17 years: 1-31 nmol/mL
> or =18 years: 3-64 nmol/mL

Myristic Acid, C14:0
<1 year: 30-320 nmol/mL
1-17 years: 40-290 nmol/mL
> or =18 years: 30-450 nmol/mL

Hexadecadienoic Acid, C16:2
<1 year: 4-27 nmol/mL
1-17 years: 3-29 nmol/mL
> or =18 years: 10-48 nmol/mL

Hexadecenoic Acid, C16:1w9
<1 year: 21-69 nmol/mL
1-17 years: 24-82 nmol/mL
> or =18 years: 25-105 nmol/mL

Palmitoleic Acid, C16:1w7
<1 year: 20-1,020 nmol/mL
1-17 years: 100-670 nmol/mL
> or =18 years: 110-1,130 nmol/mL

Palmitic Acid, C16:0
<1 year: 720-3,120 nmol/mL
1-17 years: 960-3,460 nmol/mL
> or =18 years: 1,480-3,730 nmol/mL

Gamma-Linolenic Acid, C18:3w6
<1 year: 6-110 nmol/mL
1-17 years: 9-130 nmol/mL
> or =18 years: 16-150 nmol/mL

Alpha-Linolenic Acid, C18:3w3
<1 year: 10-190 nmol/mL
1-17 years: 20-120 nmol/mL
> or =18 years: 50-130 nmol/mL

Linoleic Acid, C18:2w6

Oleic Acid, C18:1ω9
<1 year: 250-3,500 nmol/mL
1-17 years: 350-3,500 nmol/mL
≥18 years: 650-3,500 nmol/mL

Vaccenic Acid, C18:1ω7
<1 year: 140-720 nmol/mL
1-17 years: 320-900 nmol/mL
≥18 years: 280-740 nmol/mL

Stearic Acid, C18:0
<1 year: 270-1,140 nmol/mL
1-17 years: 280-1,170 nmol/mL
≥18 years: 590-1,170 nmol/mL

EPA, C20:5ω3
<1 year: 2-60 nmol/mL
1-17 years: 8-90 nmol/mL
≥18 years: 14-100 nmol/mL

Arachidonic Acid, C20:4ω6
<1 year: 110-1,110 nmol/mL
1-17 years: 350-1,030 nmol/mL
≥18 years: 520-1,490 nmol/mL

Mead Acid, C20:3ω9
< or =31 days: 8-60 nmol/mL
32 days-11 months: 3-24 nmol/mL
≥1 year: 7-30 nmol/mL

Homo-Gamma-Linolenic Acid, C20:3ω6
<1 year: 30-170 nmol/mL
1-17 years: 60-220 nmol/mL
≥18 years: 50-250 nmol/mL

Arachidic Acid, C20:0
<1 year: 30-120 nmol/mL
1-17 years: 30-90 nmol/mL
≥18 years: 50-90 nmol/mL

DHA, C22:6ω3
<1 year: 10-220 nmol/mL
1-17 years: 30-160 nmol/mL
≥18 years: 30-250 nmol/mL

DPA, C22:5ω6
<1 year: 3-70 nmol/mL
1-17 years: 10-50 nmol/mL
≥18 years: 10-70 nmol/mL

DPA, C22:5ω3
<1 year: 6-110 nmol/mL
1-17 years: 30-270 nmol/mL
> or =18 years: 20-210 nmol/mL

DTA, C22:4w6
<1 year: 2-50 nmol/mL
1-17 years: 10-40 nmol/mL
> or =18 years: 10-80 nmol/mL

Docosenoic Acid, C22:1
<1 year: 2-20 nmol/mL
> or =1 year: 4-13 nmol/mL

Docosanoic Acid, C22:0
0.0-96.3 nmol/mL

Nervonic Acid, C24:1
<1 year: 30-150 nmol/mL
1-17 years: 50-130 nmol/mL
> or =18 years: 60-100 nmol/mL

Tetracosanoic Acid, C24:0
0.0-91.4 nmol/mL

Hexacosanoic Acid, C26:1
<1 year: 0.2-2.1 nmol/mL
> or =1 year: 0.3-0.7 nmol/mL

Hexacosanoic Acid, C26:0
0.00-1.30 nmol/mL

Pristanic Acid, C15:0(CH3)4
< or =4 months: 0.00-0.60 nmol/mL
5-8 months: 0.00-0.84 nmol/mL
9-12 months: 0.00-0.77 nmol/mL
13-23 months: 0.00-1.47 nmol/mL
> or =2 years: 0.00-2.98 nmol/mL

Phytanic Acid, C16:0(CH3)4
< or =4 months: 0.00-5.28 nmol/mL
5-8 months: 0.00-5.70 nmol/mL
9-12 months: 0.00-4.40 nmol/mL
13-23 months: 0.00-8.62 nmol/mL
> or =2 years: 0.00-9.88 nmol/mL

Triene/Tetraene Ratio
< or =31 days: 0.017-0.083
32 days-17 years: 0.013-0.050
> or =18 years: 0.010-0.038

Total Saturated Acid
<1 year: 1.2-4.6 mmol/L
1-17 years: 1.4-4.9 mmol/L
> or =18 years: 2.5-5.5 mmol/L

Total Monounsaturated Acid
<1 year: 0.3-4.6 mmol/L
1-17 years: 0.5-4.4 mmol/L
> or =18 years: 1.3-5.8 mmol/L
Total Polyunsaturated Acid
<1 year: 1.1-4.9 mmol/L
1-17 years: 1.7-5.3 mmol/L
> =18 years: 3.2-5.8 mmol/L

Total w3
<1 year: 0.0-0.4 mmol/L
1-17 years: 0.1-0.5 mmol/L
> =18 years: 0.2-0.5 mmol/L

Total w6
<1 year: 0.9-4.4 mmol/L
1-17 years: 1.6-4.7 mmol/L
> =18 years: 3.0-5.4 mmol/L

Total Fatty Acids
<1 year: 3.3-14.0 mmol/L
1-17 years: 4.4-14.3 mmol/L
> =18 years: 7.3-16.8 mmol/L


FAPCP
Fatty Acid Profile, Comprehensive (C8-C26), Serum
Clinical Information: Fatty Acid Deficiency/Excess: Fats are important sources of energy for tissues and for the function and integrity of cellular membranes. Deficiencies are commonly caused by inadequate dietary intake of lipids due to an unbalanced diet, long-term parenteral nutrition, or by intestinal malabsorption. Linoleic acid, an omega-6 fatty acid, and alpha-linolenic acid, an omega-3 fatty acid, are considered essential fatty acids in that they cannot be made by the body and are essential components of the diet. The major clinical manifestations associated with essential fatty acid deficiency (EFAD) include dermatitis, increased water permeability of the skin, increased susceptibility to infection, and impaired wound healing. Biochemical abnormalities may be detected before the onset of recognizable clinical manifestations. EFAD can be detected by diminished levels of the essential fatty acids linoleic acid and alpha-linolenic acid, as well as by increases in the triene:tetraene ratio. Excess dietary fatty acids have been linked to the onset of cardiovascular disease. Elevated levels of linoleic acid can contribute to overproduction of the proinflammatory 2-series local hormones. Fatty Acid Oxidation (FAO) Disorders: Mitochondrial beta-oxidation is the main source of energy to skeletal and heart muscle during periods of fasting. When the body's supply of glucose is depleted, fatty acids are mobilized from adipose tissue and converted to ketone bodies thorough a series of steps providing an alternate source of energy. Deficient enzymes at any step in this pathway prevent the production of energy during periods of physiologic stress such as fasting or intercurrent illness. The major clinical manifestations associated with FAO disorders include hypoketotic hypoglycemia, liver disease and failure, skeletal myopathy, dilated/hypertrophic cardiomyopathy, and sudden unexpected death in early life. Signs and symptoms may vary greatly in severity, combination, and age of presentation. Life-threatening episodes of metabolic decompensation frequently occur after periods of inadequate calorie intake or intercurrent illness. When properly diagnosed, patients with FAO disorders respond favorably to fasting avoidance, diet therapy, and aggressive treatment of intercurrent illnesses, with significant reduction of morbidity and mortality. Disease-specific characteristic patterns of metabolites from FAO disorders are detectable in blood, bile, urine, and cultured fibroblasts of living and many deceased individuals. Quantitative determination of C8-C18 fatty acids is an important element of the
work-up and differential diagnosis of candidate patients. Fatty acid profiling can detect quantitatively modest, but nevertheless significant, abnormalities even when patients are asymptomatic and under dietary treatment. Confirmatory testing via the FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture and molecular analysis are also available for many of the FAO disorders at Mayo Medical Laboratories. Peroxisomal Disorders: Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include disorders of peroxisomal biogenesis with defective assembly of the entire organelle and single peroxisomal enzyme/transporter defects where the organelle is intact but a specific function is disrupted. Peroxisomal beta-oxidation of VLCFA is impaired in all disorders of peroxisomal biogenesis and in selected single enzyme deficiencies, particularly X-linked adrenoleukodystrophy, resulting in elevated concentrations of VLCFA in serum or plasma. POXP / Fatty Acid Profile, Peroxisomal (C22-C26), Plasma or POX / Fatty Acid Profile, Peroxisomal (C22-C26), Serum is the preferred screening test for evaluating patients with possible peroxisomal disorders, single-enzyme defects of peroxisomal metabolism such as X-linked adrenoleukodystrophy, or peroxisomal biogenesis disorders (Zellweger syndrome spectrum). Confirmatory testing for X-linked adrenoleukodystrophy (XALDZ / X-Linked Adrenoleukodystrophy, Full Gene Analysis) via molecular genetic analysis is available at Mayo Medical Laboratories.

Useful For: This serum test is a comprehensive profile that provides information regarding mitochondrial and peroxisomal fatty acid metabolism, and the patient's nutritional status Monitoring patients undergoing diet therapy for mitochondrial or peroxisomal disorders (possibly inducing essential fatty acid deficiency in response to restricted fat intake) Monitoring treatment of essential fatty acid deficiency Monitoring the response to provocative tests (fasting tests, loading tests)

Interpretation: An increased triene:tetraene ratio is consistent with essential fatty acid deficiency. Fatty acid oxidation disorders are recognized on the basis of disease-specific patterns that are correlated to the results of other investigations in plasma (carnitine, acylcarnitines) and urine (organic acids, acylglycines). Increased concentrations of serum very long-chain fatty acids (VLCFA) C24:0 and C26:0 are seen in peroxisomal disorders, X-linked adrenoleukodystrophy, adrenomyeloneuropathy, and Zellweger syndrome (cerebrohepatorenal syndrome). Increased concentrations of serum phytanic acid (along with normal pristanic acid concentrations) are seen in the Refsum disease (phytanase deficiency). Serum phytanic acid concentration also may be increased in other peroxisomal disorders and, when combined with the VLCFA, pristanoic acid and pipecolic acid allow differential diagnosis of peroxisomal disorders.

Reference Values:
Octanoic Acid, C8:0
<1 year: 7-63 nmol/mL
1-17 years: 9-41 nmol/mL
> or =18 years: 8-47 nmol/mL

Decenoic Acid, C10:1
<1 year: 0.8-4.8 nmol/mL
1-17 years: 1.6-6.6 nmol/mL
> or =18 years: 1.8-5.0 nmol/mL

Decanoic Acid, C10:0
<1 year: 2-62 nmol/mL
1-17 years: 3-25 nmol/mL
> or =18 years: 2-18 nmol/mL

Lauroleic Acid, C12:1
<1 year: 0.6-4.8 nmol/mL
1-17 years: 1.3-5.8 nmol/mL
> or =18 years: 1.4-6.6 nmol/mL

Lauric Acid, C12:0
<1 year: 6-190 nmol/mL
1-17 years: 5-80 nmol/mL
> or =18 years: 6-90 nmol/mL

**Tetradecadienoic Acid, C14:2**
<1 year: 0.3-6.5 nmol/mL
1-17 years: 0.2-5.8 nmol/mL
> or =18 years: 0.8-5.0 nmol/mL

**Myristoleic Acid, C14:1**
<1 year: 0.3-6.5 nmol/mL
1-17 years: 0.2-5.8 nmol/mL
> or =18 years: 0.8-5.0 nmol/mL

**Myristic Acid, C14:0**
<1 year: 30-320 nmol/mL
1-17 years: 40-290 nmol/mL
> or =18 years: 30-450 nmol/mL

**Hexadecadienoic Acid, C16:2**
<1 year: 4-27 nmol/mL
1-17 years: 3-29 nmol/mL
> or =18 years: 10-48 nmol/mL

**Hexadecenoic Acid, C16:1w9**
<1 year: 2-69 nmol/mL
1-17 years: 24-82 nmol/mL
> or =18 years: 25-105 nmol/mL

**Palmitoleic Acid, C16:1w7**
<1 year: 20-1,020 nmol/mL
1-17 years: 100-670 nmol/mL
> or =18 years: 110-1,130 nmol/mL

**Palmitic Acid, C16:0**
<1 year: 720-3,120 nmol/mL
1-17 years: 960-3,460 nmol/mL
> or =18 years: 1,480-3,730 nmol/mL

**Gamma-Linolenic Acid, C18:3w6**
<1 year: 6-110 nmol/mL
1-17 years: 9-130 nmol/mL
> or =18 years: 16-150 nmol/mL

**Alpha-Linolenic Acid, C18:3w3**
<1 year: 10-190 nmol/mL
1-17 years: 20-120 nmol/mL
> or =18 years: 50-130 nmol/mL

**Linoleic Acid, C18:2w6**
< or =31 days: 350-2,660 nmol/mL
32 days-11 months: 1,000-3,300 nmol/mL
1-17 years: 1,600-3,500 nmol/mL
> or =18 years: 2,270-3,850 nmol/mL

**Oleic Acid, C18:1w9**
<1 year: 250-3,500 nmol/mL
1-17 years: 350-3,500 nmol/mL
> or =18 years: 650-3,500 nmol/mL
Vaccenic Acid, C18:1w7
<1 year: 140-720 nmol/mL
1-17 years: 320-900 nmol/mL
> or =18 years: 280-740 nmol/mL

Stearic Acid, C18:0
<1 year: 270-1,140 nmol/mL
1-17 years: 280-1,170 nmol/mL
> or =18 years: 590-1,170 nmol/mL

EPA, C20:5w3
<1 year: 2-60 nmol/mL
1-17 years: 8-90 nmol/mL
> or =18 years: 14-100 nmol/mL

Arachidonic Acid, C20:4w6
<1 year: 110-1,110 nmol/mL
1-17 years: 350-1,030 nmol/mL
> or =18 years: 520-1,490 nmol/mL

Mead Acid, C20:3w9
< or =31 days: 8-60 nmol/mL
32 days-11 months: 3-24 nmol/mL
> or =1 year: 7-30 nmol/mL

Homo-Gamma-Linolenic Acid, C20:3w6
<1 year: 30-170 nmol/mL
1-17 years: 60-220 nmol/mL
> or =18 years: 50-250 nmol/mL

Arachidic Acid, C20:0
<1 year: 30-120 nmol/mL
1-17 years: 30-90 nmol/mL
> or =18 years: 50-90 nmol/mL

DHA, C22:6w3
<1 year: 10-220 nmol/mL
1-17 years: 30-160 nmol/mL
> or =18 years: 30-250 nmol/mL

DPA, C22:5w6
<1 year: 3-70 nmol/mL
1-17 years: 10-50 nmol/mL
> or =18 years: 10-70 nmol/mL

DPA, C22:5w3
<1 year: 6-110 nmol/mL
1-17 years: 30-270 nmol/mL
> or =18 years: 20-210 nmol/mL

DTA, C22:4w6
<1 year: 2-50 nmol/mL
1-17 years: 10-40 nmol/mL
> or =18 years: 10-80 nmol/mL

Docosenoic Acid, C22:1
<1 year: 2-20 nmol/mL
<table>
<thead>
<tr>
<th>Acid</th>
<th>&lt;1 year</th>
<th>1-17 years</th>
<th>&gt; or = 18 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docosanoic Acid, C22:0</td>
<td>4-13 nmol/mL</td>
<td>0.0-96.3 nmol/mL</td>
<td></td>
</tr>
<tr>
<td>Nervonic Acid, C24:1</td>
<td>30-150 nmol/mL</td>
<td>50-130 nmol/mL</td>
<td>60-100 nmol/mL</td>
</tr>
<tr>
<td>Tetracosanoic Acid, C24:0</td>
<td>0.0-91.4 nmol/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hexacosanoic Acid, C26:0</td>
<td>0.00-1.30 nmol/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pristanic Acid, C15:0(CH3)4</td>
<td>0.00-0.60 nmol/mL</td>
<td>0.00-0.84 nmol/mL</td>
<td>0.00-0.77 nmol/mL</td>
</tr>
<tr>
<td>Phytanic Acid, C16:0(CH3)4</td>
<td>0.00-5.28 nmol/mL</td>
<td>0.00-5.70 nmol/mL</td>
<td>0.00-4.40 nmol/mL</td>
</tr>
<tr>
<td>Triene/Tetraene Ratio</td>
<td>0.017-0.083</td>
<td>0.013-0.050</td>
<td>0.010-0.038</td>
</tr>
<tr>
<td>Total Saturated Acid</td>
<td>1.2-4.6 mmol/L</td>
<td>1.4-4.9 mmol/L</td>
<td>2.5-5.5 mmol/L</td>
</tr>
<tr>
<td>Total Monounsaturated Acid</td>
<td>0.3-4.6 mmol/L</td>
<td>0.5-4.4 mmol/L</td>
<td>1.3-5.8 mmol/L</td>
</tr>
<tr>
<td>Total Polyunsaturated Acid</td>
<td>1.1-4.9 mmol/L</td>
<td>1.7-5.3 mmol/L</td>
<td>3.2-5.8 mmol/L</td>
</tr>
<tr>
<td>Total w3</td>
<td>0.0-0.4 mmol/L</td>
<td>0.1-0.5 mmol/L</td>
<td>0.2-0.5 mmol/L</td>
</tr>
</tbody>
</table>
Total w6
<1 year: 0.9-4.4 mmol/L
1-17 years: 1.6-4.7 mmol/L
> or =18 years: 3.0-5.4 mmol/L

Total Fatty Acids
<1 year: 3.3-14.0 mmol/L
1-17 years: 4.4-14.3 mmol/L
> or =18 years: 7.3-16.8 mmol/L

Clinical References:

Clinical Information:
Fats are important sources of energy for tissues and for the function and integrity of cellular membranes. Deficiencies are commonly caused by inadequate dietary intake of lipids due to an unbalanced diet, long-term parenteral nutrition, or by intestinal malabsorption. Linoleic acid, an omega-6 fatty acid, and alpha-linolenic acid, an omega-3 fatty acid, are considered essential fatty acids in that they cannot be made by the body and are essential components of the diet. The major clinical manifestations associated with essential fatty acid deficiency (EFAD) include dermatitis, increased water permeability of the skin, increased susceptibility to infection, and impaired wound healing. Biochemical abnormalities may be detected before the onset of recognizable clinical manifestations. EFAD can be detected by diminished levels of the essential fatty acids linoleic acid and alpha-linolenic acid, as well as by increases in the triene:tetraene ratio. Excess dietary fatty acids have been linked to the onset of cardiovascular disease. Elevated levels of linoleic acid can contribute to overproduction of the proinflammatory 2-series local hormones.

Useful For:
- Evaluating the nutritional intake and intestinal absorption of essential fatty acids
- Identifying deficiency of essential and other nutritionally beneficial fatty acids
- Monitoring treatment of patients with essential fatty acid deficiencies who are receiving linoleic acid (C18:2w6) and alpha-linolenic acid (C18:3w3)

Interpretation:
Concentrations below the stated reference ranges are consistent with fatty acid deficiencies. An increased triene:tetraene ratio is consistent with essential fatty acid deficiency

Reference Values:
Lauric Acid, C12:0
<1 year: 6-190 nmol/mL
1-17 years: 5-80 nmol/mL
> or =18 years: 6-90 nmol/mL

Myristic Acid, C14:0
<1 year: 30-320 nmol/mL
1-17 years: 40-290 nmol/mL
> or =18 years: 30-450 nmol/mL

Hexadecenoic Acid, C16:1w9
<1 year: 21-69 nmol/mL
1-17 years: 24-82 nmol/mL
> or =18 years: 25-105 nmol/mL

Palmitoleic Acid, C16:1w7
<1 year: 20-1,020 nmol/mL
1-17 years: 100-670 nmol/mL
Palmitic Acid, C16:0
<1 year: 720-3,120 nmol/mL
1-17 years: 960-3,460 nmol/mL
> or =18 years: 1,480-3,730 nmol/mL

Gamma-Linolenic Acid, C18:3w6
<1 year: 6-110 nmol/mL
1-17 years: 9-130 nmol/mL
> or =18 years: 16-150 nmol/mL

Alpha-Linolenic Acid, C18:3w3
<1 year: 10-190 nmol/mL
1-17 years: 20-120 nmol/mL
> or =18 years: 50-130 nmol/mL

Linoleic Acid, C18:2w6
< or =31 days: 350-2,660 nmol/mL
32 days-11 months: 1,000-3,300 nmol/mL
1-17 years: 1,600-3,500 nmol/mL
> or =18 years: 2,270-3,850 nmol/mL

Oleic Acid, C18:1w9
<1 year: 250-3,500 nmol/mL
1-17 years: 350-3,500 nmol/mL
> or =18 years: 650-3,500 nmol/mL

Vaccenic Acid, C18:1w7
<1 year: 140-720 nmol/mL
1-17 years: 320-900 nmol/mL
> or =18 years: 280-740 nmol/mL

Stearic Acid, C18:0
<1 year: 270-1,140 nmol/mL
1-17 years: 280-1,170 nmol/mL
> or =18 years: 590-1,170 nmol/mL

EPA, C20:5w3
<1 year: 2-60 nmol/mL
1-17 years: 8-90 nmol/mL
> or =18 years: 14-100 nmol/mL

Arachidonic Acid, C20:4w6
<1 year: 110-1,110 nmol/mL
1-17 years: 350-1,030 nmol/mL
> or =18 years: 520-1,490 nmol/mL

Mead Acid, C20:3w9
< or =31 days: 8-60 nmol/mL
32 days-11 months: 3-24 nmol/mL
1-17 years: 7-30 nmol/mL
> or =18 years: 7-30 nmol/mL

Homo-Gamma-Linolenic C20:3w6
<1 year: 30-170 nmol/mL
1-17 years: 60-220 nmol/mL
> or =18 years: 50-250 nmol/mL
Arachidic Acid, C20:0
<1 year: 30-120 nmol/mL
1-17 years: 30-90 nmol/mL
> or =18 years: 50-90 nmol/mL

DHA, C22:6w3
<1 year: 10-220 nmol/mL
1-17 years: 30-160 nmol/mL
> or =18 years: 30-250 nmol/mL

DPA, C22:5w3
<1 year: 3-70 nmol/mL
1-17 years: 10-50 nmol/mL
> or =18 years: 10-70 nmol/mL

DPA, C22:5w6
<1 year: 6-110 nmol/mL
1-17 years: 30-270 nmol/mL
> or =18 years: 20-210 nmol/mL

DTA, C22:4w6
<1 year: 2-50 nmol/mL
1-17 years: 10-40 nmol/mL
> or =18 years: 10-80 nmol/mL

Docosenoic Acid, C22:1
<1 year: 2-20 nmol/mL
1-17 years: 4-13 nmol/mL
> or =18 years: 4-13 nmol/mL

Nervonic Acid, C24:1w9
<1 year: 30-150 nmol/mL
1-17 years: 50-130 nmol/mL
> or =18 years: 60-100 nmol/mL

Triene/Tetraene Ratio
< or =31 days: 0.017-0.083
32 days-17 years: 0.013-0.050
> or =18 years: 0.010-0.038

Total Saturated Acid
<1 year: 1.2-4.6 mmol/L
1-17 years: 1.4-4.9 mmol/L
> or =18 years: 2.5-5.5 mmol/L

Total Monounsaturated Acid
<1 year: 0.3-4.6 mmol/L
1-17 years: 0.5-4.4 mmol/L
> or =18 years: 1.3-5.8 mmol/L

Total Polyunsaturated Acid
<1 year: 1.1-4.9 mmol/L
1-17 years: 1.7-5.3 mmol/L
> or =18 years: 3.2-5.8 mmol/L

Total w3
<1 year: 0.0-0.4 mmol/L
FAPEP
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Fatty Acid Profile, Essential, Serum

Clinical Information: Fats are important sources of energy for tissues and for the function and integrity of cellular membranes. Deficiencies are commonly caused by inadequate dietary intake of lipids due to an unbalanced diet, long-term parenteral nutrition, or by intestinal malabsorption. Linoleic acid, an omega-6 fatty acid, and alpha-linolenic acid, an omega-3 fatty acid, are considered essential fatty acids in that they cannot be made by the body and are essential components of the diet. The major clinical manifestations associated with essential fatty acid deficiency (EFAD) include dermatitis, increased water permeability of the skin, increased susceptibility to infection, and impaired wound healing. Biochemical abnormalities may be detected before the onset of recognizable clinical manifestations. EFAD can be detected by diminished levels of the essential fatty acids linoleic acid and alpha-linolenic acid, as well as by increases in the triene:tetraene ratio. Excess dietary fatty acids have been linked to the onset of cardiovascular disease. Elevated levels of linoleic acid can contribute to overproduction of the proinflammatory 2-series local hormones.

Useful For: Evaluating the nutritional intake and intestinal absorption of essential fatty acids
Identifying deficiency of essential and other nutritionally beneficial fatty acids Monitoring treatment of patients with essential fatty acid deficiencies who are receiving linoleic acid (C18:2w6) and alpha-linolenic acid (C18:3w3)

Interpretation: Concentrations below the stated reference ranges are consistent with fatty acid deficiencies. An increased triene:tetraene ratio is consistent with essential fatty acid deficiency.

Reference Values:
Lauric Acid, C12:0
<1 year: 6-190 nmol/mL
1-17 years: 5-80 nmol/mL
> or =18 years: 6-90 nmol/mL

Myristic Acid, C14:0
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> or =18 years: 30-450 nmol/mL

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<1 year: 21-69 nmol/mL
1-17 years: 24-82 nmol/mL
> or =18 years: 25-105 nmol/mL

Palmitoleic Acid, C16:1w7
<1 year: 20-1,020 nmol/mL
1-17 years: 100-670 nmol/mL
> or =18 years: 110-1,130 nmol/mL

Palmitic Acid, C16:0
<1 year: 720-3,120 nmol/mL
1-17 years: 960-3,460 nmol/mL
> or =18 years: 1,480-3,730 nmol/mL

Gamma-Linolenic Acid, C18:3w6
<1 year: 6-110 nmol/mL
1-17 years: 9-130 nmol/mL
> or =18 years: 16-150 nmol/mL

Alpha-Linolenic Acid, C18:3w3
<1 year: 10-190 nmol/mL
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Linoleic Acid, C18:2w6
< or =31 days: 350-2,660 nmol/mL
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> or =18 years: 280-740 nmol/mL

Stearic Acid, C18:0
<1 year: 270-1,140 nmol/mL
1-17 years: 280-1,170 nmol/mL
> or =18 years: 590-1,170 nmol/mL

EPA, C20:5w3
<1 year: 2-60 nmol/mL
1-17 years: 8-90 nmol/mL
> or =18 years: 14-100 nmol/mL

Arachidonic Acid, C20:4w6
<1 year: 110-1,110 nmol/mL
1-17 years: 350-1,030 nmol/mL
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Mead Acid, C20:3w9
< or =31 days: 8-60 nmol/mL
32 days-11 months: 3-24 nmol/mL
1-17 years: 7-30 nmol/mL
> or =18 years: 7-30 nmol/mL

Homo-Gamma-Linolenic C20:3w6
<1 year: 30-170 nmol/mL
1-17 years: 60-220 nmol/mL
> or =18 years: 50-250 nmol/mL

Arachidic Acid, C20:0
<1 year: 30-120 nmol/mL
1-17 years: 30-90 nmol/mL
> or =18 years: 50-90 nmol/mL

DHA, C22:6w3
<1 year: 10-220 nmol/mL
1-17 years: 30-160 nmol/mL
> or =18 years: 30-250 nmol/mL

DPA, C22:5w6
<1 year: 3-70 nmol/mL
1-17 years: 10-50 nmol/mL
> or =18 years: 10-70 nmol/mL

DPA, C22:5w3
<1 year: 6-110 nmol/mL
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> or =18 years: 20-210 nmol/mL

DTA, C22:4w6
<1 year: 2-50 nmol/mL
1-17 years: 10-40 nmol/mL
> or =18 years: 10-80 nmol/mL

Docosenoic Acid, C22:1
<1 year: 2-20 nmol/mL
1-17 years: 4-13 nmol/mL
> or =18 years: 4-13 nmol/mL

Nervonic Acid, C24:1w9
<1 year: 30-150 nmol/mL
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Triene/Tetraene Ratio
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Total Saturated Acid
<1 year: 1.2-4.6 mmol/L
1-17 years: 1.4-4.9 mmol/L
> or =18 years: 2.5-5.5 mmol/L

Total Monounsaturated Acid
<1 year: 0.3-4.6 mmol/L
1-17 years: 0.5-4.4 mmol/L
> or =18 years: 1.3-5.8 mmol/L

Total Polyunsaturated Acid
<1 year: 1.1-4.9 mmol/L
1-17 years: 1.7-5.3 mmol/L
> or =18 years: 3.2-5.8 mmol/L
Total w3
<1 year: 0.0-0.4 mmol/L
1-17 years: 0.1-0.5 mmol/L
> or =18 years: 0.2-0.5 mmol/L

Total w6
<1 year: 0.9-4.4 mmol/L
1-17 years: 1.6-4.7 mmol/L
> or =18 years: 3.0-5.4 mmol/L

Total Fatty Acids
<1 year: 3.3-14.0 mmol/L
1-17 years: 4.4-14.3 mmol/L
> or =18 years: 7.3-16.8 mmol/L


Fatty Acid Profile, Mitochondrial (C8-C18), Serum

Clinical Information: Mitochondrial beta-oxidation is the main source of energy to skeletal and heart muscle during periods of fasting. When the body's supply of glucose is depleted, fatty acids are mobilized from adipose tissue and converted to ketone bodies thorough a series of steps providing an alternate source of energy. Deficient enzymes at any step in this pathway prevent the production of energy during periods of physiologic stress such as fasting or intercurrent illness. The major clinical manifestations associated with fatty acid oxidation (FAO) disorders include hypoketotic hypoglycemia, liver disease and failure, skeletal myopathy, dilated/hypertrophic cardiomyopathy, and sudden unexpected death in early life. Signs and symptoms may vary greatly in severity, combination and age of presentation. Life-threatening episodes of metabolic decompensation frequently occur after periods of inadequate calorie intake or intercurrent illness. When properly diagnosed, patients with FAO disorders respond favorably to fasting avoidance, diet therapy, and aggressive treatment of intercurrent illnesses, with significant reduction of morbidity and mortality. Disease-specific characteristic patterns of metabolites from FAO disorders are detectable in blood, bile, urine, and cultured fibroblasts of living and many deceased individuals. Quantitative determination of C8-C18 fatty acids is an important element of the workup and differential diagnosis of candidate patients. Fatty acid profiling can detect quantitatively modest, but nevertheless significant, abnormalities even when patients are asymptomatic and under dietary treatment. Confirmatory testing via FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture and molecular analysis are also available for many of the FAO disorders at Mayo Medical Laboratories.

Useful For: Biochemical diagnosis of inborn errors of mitochondrial fatty acid oxidation, including deficiencies of medium-chain acyl-Co-A dehydrogenase, long-chain 3-hydroxyacyl-Co-A dehydrogenase, very long-chain acyl-Co-A dehydrogenase, and glutaricacidemia type 2

Interpretation: Fatty acid oxidation disorders are recognized on the basis of disease-specific metabolite patterns that are correlated to the results of other investigations in plasma (carnitine, acylcarnitines) and urine (organic acids, acylglycines).

Reference Values:
Octanoic Acid, C8:0
<1 year: 7-63 nmol/mL
1-17 years: 9-41 nmol/mL
> or =18 years: 8-47 nmol/mL

Decenoic Acid, C10:1
<1 year: 0.8-4.8 nmol/mL
1-17 years: 1.6-6.6 nmol/mL
Decanoic Acid, C10:0
< 1 year: 2-62 nmol/mL
1-17 years: 3-25 nmol/mL
> or =18 years: 2-18 nmol/mL

Lauroleic Acid, C12:1
< 1 year: 0.6-4.8 nmol/mL
1-17 years: 1.3-5.8 nmol/mL
> or =18 years: 1.4-6.6 nmol/mL

Lauric Acid, C12:0
< 1 year: 6-190 nmol/mL
1-17 years: 5-80 nmol/mL
> or =18 years: 6-90 nmol/mL

Tetradecadienoic Acid, C14:2
< 1 year: 0.3-6.5 nmol/mL
1-17 years: 0.2-5.8 nmol/mL
> or =18 years: 0.8-5.0 nmol/mL

Myristoleic Acid, C14:1
< 1 year: 1-46 nmol/mL
1-17 years: 1-31 nmol/mL
> or =18 years: 3-64 nmol/mL

Myristic Acid, C14:0
< 1 year: 30-320 nmol/mL
1-17 years: 40-290 nmol/mL
> or =18 years: 30-450 nmol/mL

Hexadecadienoic Acid, C16:2
< 1 year: 4-27 nmol/mL
1-17 years: 3-29 nmol/mL
> or =18 years: 10-48 nmol/mL

Palmitoleic Acid, C16:1w7
< 1 year: 20-1,020 nmol/mL
1-17 years: 100-670 nmol/mL
> or =18 years: 110-1,130 nmol/mL

Palmitic Acid, C16:0
< 1 year: 720-3,120 nmol/mL
1-17 years: 960-3,460 nmol/mL
> or =18 years: 1,480-3,730 nmol/mL

Linoleic Acid, C18:2w6
< or =31 days: 350-2,660 nmol/mL
32 days-11 months: 1,000-3,300 nmol/mL
1-17 years: 1,600-3,500 nmol/mL
> or =18 years: 2,270-3,850 nmol/mL

Oleic Acid, C18:1w9
< 1 year: 250-3,500 nmol/mL
1-17 years: 350-3,500 nmol/mL
> or =18 years: 650-3,500 nmol/mL
Stearic Acid, C18:0
<1 year: 270-1,140 nmol/mL
1-17 years: 280-1,170 nmol/mL
≥18 years: 590-1,170 nmol/mL


POXP 60468

Fatty Acid Profile, Peroxisomal (C22-C26), Plasma

Clinical Information: Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include disorders of peroxisomal biogenesis with defective assembly of the entire organelle and single peroxisomal enzyme/transporter defects where the organelle is intact but a specific function is disrupted. Peroxisomal beta-oxidation of VLCFA is impaired in all disorders of peroxisomal biogenesis and in selected single enzyme deficiencies, particularly X-linked adrenoleukodystrophy (X-ALD), resulting in elevated concentrations of VLCFA in plasma or serum. Peroxisomal biogenesis disorders (PBD) include the Zellweger syndrome spectrum disorders that are clinically diverse and range in severity from neonatal lethal (Zellweger syndrome) to more variable clinical courses in neonatal adrenoleukodystrophy and infantile Refsum disease. Affected children typically have hypotonia, poor feeding, distinctive facial features, seizures, and liver dysfunction. Other features can include retinal dystrophy, hearing loss, developmental delays, and bleeding episodes. Rhizomelic chondrodysplasia punctata is another PBD. It is characterized by rhizomelic shortening, chondrodysplasia punctata, cataracts, intellectual disability, and seizures, although it can have a milder phenotype with only cataracts and chondrodysplasia. The typical biochemical profile shows normal VLCFA and elevated phytanic acid. X-ALD is a neurologic disorder affecting the white matter and adrenal cortex. It can present between ages 4 and 8 as a childhood cerebral form with behavioral and cognitive changes, associated with neurologic decline. Other forms include an "Addison disease only" phenotype with adrenocortical insufficiency without initial neurologic abnormality and adrenomyeloneuropathy associated with later-onset progressive paraparesis. X-ALD is an X-linked condition that primarily affects males; however, some females who are carriers can develop later-onset neurologic manifestations. In 2016, X-ALD was added to the US Recommended Uniform Screening Panel (RUSP), a list of conditions that are nationally recommended for newborn screening by the Secretaryâ€™s Advisory Committee on Heritable Disorders in Newborns and Children. Refsum disease is a peroxisomal disorder characterized by anosmia, retinitis pigmentosa, neuropathy, deafness, ataxia, ichthyosis, and cardiac abnormalities. The classic biochemical profile of Refsum disease is an elevated plasma or serum phytanic acid level. Biochemical abnormalities in peroxisomal disorders include accumulations of VLCFA, phytanic, and pristanic acid. The differential diagnosis of these disorders is based on recognition of clinical phenotypes combined with a series of biochemical tests to assess peroxisomal function and structure. These include measurements and ratios of VLCFA, piperolic acid (PIPA / Picroelic Acid, Serum; PipU / Picroelic Acid, Urine), phytanic acid and its metabolite pristanic acid. In addition, confirmatory testing for X-linked adrenoleukodystrophy (XALDZ / X-Linked Adrenoleukodystrophy, Full Gene Analysis) via molecular genetic analysis is available at Mayo Medical Laboratories.

Useful For: Evaluating patients with possible peroxisomal disorders, including peroxisomal biogenesis disorders, X-linked adrenoleukodystrophy, and Refsum disease An aid in the assessment of peroxisomal function

Interpretation: Reports include concentrations of C22:0, C24:0, C26:0 species, phytanic acid and pristanic acid, and calculated C24:0/C22:0, C26:0/C22:0, and phytanic acid:pristanic acid ratios. When no significant abnormalities are detected, a simple descriptive interpretation is provided. A profile of elevated phytanic acid, low-normal pristanic acid, and normal very long-chain fatty acids is suggestive of Refsum disease (phytanic acid oxidase deficiency); however, phytanic acid concentration may also be increased in disorders of peroxisomal biogenesis and should be considered in the differential diagnosis of peroxisomal disorders. If results are suggestive of hemizygosity for X-linked adrenoleukodystrophy, we also include the calculated value of a discriminating function used to more accurately segregate hemizygous
individuals from normal controls. Positive test results could be due to a genetic or nongenetic condition. Additional confirmatory testing would be required to differentiate between these causes.

**Reference Values:**

C22:0
< or =96.3 nmol/mL

C24:0
< or =91.4 nmol/mL

C26:0
< or =1.30 nmol/mL

C24:0/C22:0 RATIO
< or =1.39

C26:0/C22:0 RATIO
< or =0.023

PRISTANIC ACID
0-4 months: < or =0.60 nmol/mL
5-8 months: < or =0.84 nmol/mL
9-12 months: < or =0.77 nmol/mL
13-23 months: < or =1.47 nmol/mL
> or =24 months: < or =2.98 nmol/mL

PHYTANIC ACID
0-4 months: < or =5.28 nmol/mL
5-8 months: < or =5.70 nmol/mL
9-12 months: < or =4.40 nmol/mL
13-23 months: < or =8.62 nmol/mL
> or =24 months: < or =9.88 nmol/mL

PRISTANIC/PHYTANIC ACID RATIO
0-4 months: < or =0.35
5-8 months: < or =0.28
9-12 months: < or =0.23
13-23 months: < or =0.24
> or =24 months: < or =0.39


**Fatty Acid Profile, Peroxisomal (C22-C26), Serum**

**Clinical Information:** Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogens and bile acids. Peroxisomal disorders include disorders of peroxisomal biogenesis with defective assembly of the entire organelle and single peroxisomal enzyme/transporter defects where the organelle is intact but a specific function is disrupted. Peroxisomal beta-oxidation of VLCFA is impaired in all disorders of peroxisomal biogenesis and in selected single enzyme deficiencies, particularly X-linked adrenoleukodystrophy (X-ALD), resulting in elevated concentrations of VLCFA in plasma or serum. Peroxisomal biogenesis disorders (PBD) include the Zellweger syndrome spectrum disorders that are clinically diverse and
range in severity from neonatal lethal (Zellweger syndrome) to more variable clinical courses in
neonatal adrenoleukodystrophy and infantile Refsum disease. Affected children typically have
hypotonia, poor feeding, distinctive facial features, seizures, and liver dysfunction. Other features can
include retinal dystrophy, hearing loss, developmental delays, and bleeding episodes. Rhizomelic
chondrodysplasia punctata is another PBD. It is characterized by rhizomelic shortening,
chondrodysplasia punctata, cataracts, intellectual disability, and seizures, although it can have a milder
phenotype with only cataracts and chondrodysplasia. The typical biochemical profile shows normal
VLCFA and elevated phytanic acid. X-ALD is a neurologic disorder affecting the white matter and
adrenal cortex. It can present between ages 4 and 8 as a childhood cerebral form with behavioral and
cognitive changes, associated with neurologic decline. Other forms include an "Addison disease only"
phenotype with adrenocortical insufficiency without initial neurologic abnormality and
adrenomyeloneuropathy associated with later-onset progressive paraparesis. X-ALD is an X-linked
condition that primarily affects males; however, some females who are carriers can develop later-onset
neurologic manifestations. In 2016, X-ALD was added to the US Recommended Uniform Screening
Panel (RUSP), a list of conditions that are nationally recommended for newborn screening by the
Secretaryâ€™s Advisory Committee on Heritable Disorders in Newborns and Children. Refsum disease
is a peroxisomal disorder characterized by anosmia, retinitis pigmentosa, neuropathy, deafness, ataxia,
ichthyosis, and cardiac abnormalities. The classic biochemical profile of Refsum disease is an elevated
plasma or serum phytanic acid level. Biochemical abnormalities in peroxisomal disorders include
accumulations of VLCFA, phytanic, and pristanic acid. The differential diagnosis of these disorders is
based on recognition of clinical phenotypes combined with a series of biochemical tests to assess
peroxisomal function and structure. These include measurements and ratios of VLCFA, piperolic acid
(PIPA / Pipline Acid, Serum; PIPU / Pipelic Acid, Urine), phytanic acid and its metabolite pristanic
acid. In addition, confirmatory testing for X-linked adrenoleukodystrophy (XALDZ / X-Linked
Adrenoleukodystrophy, Full Gene Analysis) via molecular genetic analysis is available at Mayo
Medical Laboratories.

**Useful For:** Evaluating patients with possible peroxisomal disorders, single-enzyme defects of
peroxisomal metabolism such as X-linked adrenoleukodystrophy or peroxisomal biogenesis disorders
(Zellweger syndrome spectrum) An aid in the assessment of peroxisomal function

**Interpretation:** Reports include concentrations of C22:0, C24:0, C26:0 species, phytanic acid and
pristanic acid, and calculated C24:0/C22:0, C26:0/C22:0, and phytanic acid:pristanic acid ratios. When no
significant abnormalities are detected, a simple descriptive interpretation is provided. A profile of elevated
phytanic acid, low-normal pristanic acid, and normal very long-chain fatty acids is suggestive of Refsum
disease (phytanic acid oxidase deficiency); however, serum phytanic acid concentration may also be
increased in disorders of peroxisomal biogenesis and should be considered in the differential diagnosis of
peroxisomal disorders. If results are suggestive of hemizygosity for X-linked adrenoleukodystrophy, we
also include the calculated value of a discriminating function used to more accurately segregate
hemizygous individuals from normal controls. Positive test results could be due to a genetic or nongenetic
condition. Additional confirmatory testing would be required to differentiate between these causes.

**Reference Values:**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>C22:0</td>
<td>&lt; or =96.3 nmol/mL</td>
</tr>
<tr>
<td>C24:0</td>
<td>&lt; or =91.4 nmol/mL</td>
</tr>
<tr>
<td>C26:0</td>
<td>&lt; or =1.30 nmol/mL</td>
</tr>
<tr>
<td>C24:0/C22:0 RATIO</td>
<td>&lt; or =1.39</td>
</tr>
<tr>
<td>C26:0/C22:0 RATIO</td>
<td>&lt; or =0.023</td>
</tr>
</tbody>
</table>

**PRISTANIC ACID**
0-4 months: < or =0.60 nmol/mL
5-8 months: < or =0.84 nmol/mL
9-12 months: < or =0.77 nmol/mL
13-23 months: < or =1.47 nmol/mL
> or =24 months: < or =2.98 nmol/mL

PHYTANIC ACID
0-4 months: < or =5.28 nmol/mL
5-8 months: < or =5.70 nmol/mL
9-12 months: < or =4.40 nmol/mL
13-23 months: < or =8.62 nmol/mL
> or =24 months: < or =9.88 nmol/mL

PRISTANIC/PHYTANIC ACID RATIO
0-4 months: < or =0.35
5-8 months: < or =0.28
9-12 months: < or =0.23
13-23 months: < or =0.24
> or =24 months: < or =0.39


FBN1 Full Gene Sequence, Varies

Clinical Information: Fibrillin-1 is a 320-kD cysteine-rich glycoprotein found in the extracellular matrix. Monomers of fibrillin-1 associate to form microfibrils that provide mechanical stability and elastic properties to connective tissues. Fibrillin-1 is encoded by the FBN1 gene, which contains 65 exons and is located at chromosome 15q21. Pathogenic FBN1 variants are most commonly associated with Marfan syndrome (MFS), an autosomal dominant connective tissue disorder involving the ocular, skeletal, and cardiovascular systems. Ocular MFS manifestations most commonly include myopia and lens displacement. Skeletal manifestations can include arachnodactyly (abnormally long and slender fingers and toes), dolichostenomelia (long limbs), pectus (chest wall) deformity, and scoliosis. Cardiovascular manifestations, which are the major cause of early morbidity and mortality in MFS, include aortic aneurysm and dissection, as well as mitral valve and tricuspid valve prolapse. There is significant inter- and intrafamilial variability in the MFS phenotype. Pathogenic FBN1 variants have also been reported in several other rare phenotypes with variable overlap with classic MFS. In some cases, MFS may present in the neonatal period with severe, rapidly progressive disease (previously termed "neonatal Marfan syndrome"). Other FBN1-associated conditions include autosomal dominant ectopia lentis (displacement of the lens of the eye), familial thoracic aortic aneurysm and dissection, isolated skeletal features of MFS, MASS phenotype (mitral valve prolapse, aortic diameter increased, stretch marks, skeletal features of MFS), Shprintzen-Goldberg syndrome (Marfanoid-craniosynostosis; premature ossification and closure of sutures of the skull), and autosomal dominant Weill-Marchesani syndrome (short stature, short fingers, ectopia lentis). Hundreds of pathogenic variants have been identified in FBN1, many of them unique to individual families. There is a wide range of variability, including intrafamilial variability, in expressivity among pathogenic FBN1 variants. Approximately two-thirds of pathogenic FBN1 variants are missense changes, with the majority of these being cysteine substitutions. Approximately 25% to 33% of pathogenic FBN1 variants are de novo, in which an individual has no family history of disease. Pathogenic FBN1 variants have been shown to occur across the gene. Some genotype-phenotype correlations have been observed, including the association with truncating and splicing variants with risk for aortic dissection, cysteine-based variants, and ectopia lentis, and severe, early onset MFS and variants in exons 24 through 32. Marfan syndrome has significant clinical overlap with a condition called Loeys-Dietz syndrome (LDS); however, the vascular phenotype of LDS can be more severe, and LDS is caused by pathogenic variants in different genes.
When the diagnosis of MFS, LDS, or a related disorder is suspected, the use of genetic testing is important to verify the diagnosis and provide appropriate clinical management. Confirmation of the genetic diagnosis also allows for preconception, prenatal, and family counseling.

**Useful For:** Aiding in the diagnosis of:  
- FBN1-associated Marfan syndrome  
- Autosomal dominant ectopia lentis  
- Isolated ascending aortic aneurysm and dissection  
- Isolated skeletal features of Marfan syndrome  
- MASS phenotype (mitral valve prolapse, aortic diameter increased, stretch marks, skeletal features of MFS)  
- Shprintzen-Goldberg syndrome  
- Autosomal dominant Weill-Marchesani syndrome

**Interpretation:** Evaluation and categorization of variants is performed using American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment. Unless reported or predicted to impact splicing, alterations found deep in the intron or alterations that do not result in an amino acid substitution are not reported.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Feather Panel # 2**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Aiding in the diagnosis of an allergic disease and defining the allergens responsible for eliciting signs and symptoms Identifying allergens that may be responsible for allergic disease and/or anaphylactic episode, confirming sensitization to particular allergens prior to beginning immunotherapy, and investigating the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.


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**LEU 8046**

**Fecal Leukocytes**

**Clinical Information:** Leukocytes are not normally seen in stools in the absence of infection or other inflammatory processes. Fecal leukocytosis is a response to infection with microorganisms that invade tissue or produce toxins, which causes tissue damage. Fecal leukocytes are commonly found in patients with shigellosis and salmonellosis (erythrocytes) and sometimes in amebiasis. Mononuclear cells are found in typhoid fever. Ulcerative colitis may also be associated with fecal leukocytosis.

**Useful For:** Suggesting presence of pathogens such as Salmonella, Shigella, and amebiasis

**Interpretation:** When fecal leukocytes are found they are reported in a semiquantitative manner: "few" indicates < or = 2/oil immersion microscopic field (OIF); "moderate" indicates 3/OIF to 9/OIF; "many" indicates > or = 10/OIF. The greater the number of leukocytes, the greater the likelihood that an invasive pathogen is present. The finding of many fecal leukocytes is a good indicator of the presence of an invasive microbiological pathogen such as Salmonella or Shigella. Few or no leukocytes and many erythrocytes suggests amebiasis. Fecal leukocytes are rarely seen in diarrheas caused by other parasites or viruses.

**Reference Values:**
Interpretive report


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**FOBT 60693**

**Fecal Occult Blood, Colorectal Cancer Screen, Qualitative, Immunochemical**

**Clinical Information:** Colorectal cancer (CRC) is 1 of the most commonly diagnosed cancers in the United States (US), and the second leading cause of cancer-related deaths. CRC almost always develops from adenomatous polyps, yet patients remain asymptomatic until the cancer progresses to a fairly advanced stage. Screening for colorectal cancer is strongly advocated for by the US Preventive Services Task Force, the American Cancer Society, the American College of Gastroenterology, and other clinical societies, due to the high incidence of disease and decrease in mortality with medical intervention. Men and women at average risk for colorectal cancer should be screened at regular
intervals beginning at age 50, continuing until age 75. Individuals with certain high-risk factors (age, African-American race, inflammatory intestinal disorders, family history of colon cancer, obesity, diabetes, poor diet) may consider earlier screening strategies. Several options are available for CRC screening and includes fecal occult blood testing (FOBT), sigmoidoscopy, and colonoscopy. FOBT historically utilized guaiac-based tests that identify the presence of hemoglobin based on a nonspecific peroxidase reaction. Guaiac-based FOBT is no longer recommended for cancer screening because it does not detect most polyps and cancers. Furthermore, the false-positive rate with guaiac tests is high if patients do not follow the recommended dietary (withholding notably meat, certain vegetables, iron supplements) or pharmaceutical (withholding nonsteroidal anti-inflammatory drugs, vitamin C) restrictions. Finally, multiple stool collections are needed for optimal interpretation of guaiac-based FOBT results. Fecal immunochemical testing (FIT) has evolved as the preferred occult blood test for colorectal cancer screening due to the lack of specificity and sensitivity of guaiac-based methods. FIT specifically detects the presence of human hemoglobin, eliminating the need for dietary and medication restrictions. For colorectal cancer screening only a single collection is required. The specificity of FIT is routinely >95% with reported sensitivities ranging from 40% to 70% based on the patient population. The clinical specificity of FIT is 97% based on internal studies conducted at Mayo. To evaluate occult GI bleeding in patients with anemia or iron deficiency, the HemoQuant test should be used (HQ / HemoQuant, Feces). Neither FIT nor guaiac testing detects upper gastrointestinal (GI) bleeding because globin and heme are degraded during intestinal transit. In contrast, the HemoQuant test detects occult bleeding equally well from all sources within the GI tract. The HemoQuant test utilizes a specific fluorometric method that will detect any hemoglobin or heme-derived porphyrins in the stool, is very sensitive, and provides quantitative results.

**Useful For:** Colorectal cancer screening Screening for gastrointestinal bleeding

**Interpretation:** This is a quantitative assay but results are reported qualitatively as negative or positive for the presence of fecal occult blood; the cutoff for positivity is 100 ng/mL hemoglobin. The following comments will be reported with the qualitative result for patients >17 years: - Positive results; further testing is recommended if clinically indicated. This test has 97% specificity for detection of lower gastrointestinal bleeding in colorectal cancer. - Negative results; this test will not detect upper gastrointestinal bleeding; HQ / HemoQuant, Feces test should be ordered if clinically indicated.

**Reference Values:**
Negative

This test has not been validated in a pediatric population, results should be interpreted in the context of the patient’s presentation.


**FELBA**

**FELBA 80782**

**Felbamate (Felbatol), Serum**

**Clinical Information:** Felbamate is an anticonvulsant drug approved for treatment of partial seizures with or without secondary generalization in persons >14 years of age. It is also approved for Lennox-Gastaut syndrome in children >2 years of age. Felbamate is well absorbed (>90%) and is metabolized by the hepatic cytochrome P450 system. Metabolites lack anticonvulsant activity. The elimination half-life of felbamate ranges from 13 to 23 hours. Optimal response to felbamate is seen with
serum concentrations between 30 mcg/mL to 60 mcg/mL. Patients who are elderly or have renal
dysfunction may require reduced dosing; felbamate should not be given to individuals with hepatic
disease. Toxicity can be severe, including life-threatening aplastic anemia or liver failure, but no defined
toxic concentration has been established. Coadministration of felbamate increases the concentration of
phenytoin and valproic acid, decreases carbamazepine concentration, and increases
carbamazepine-10,11-epoxide (its active metabolite). Conversely, coadministration of phenytoin or
carbamazepine causes a decrease in felbamate concentration.

**Useful For:** Determining whether a poor therapeutic response is attributable to noncompliance or
lack of drug effectiveness Monitoring changes in serum concentrations resulting from interactions with
coadministered drugs such as barbiturates and phenytoin

**Interpretation:** Optimal response to felbamate is associated with serum concentrations of 30
mcg/mL to 60 mcg/mL. Toxic serum concentrations for felbamate have not been established.

**Reference Values:**
30.0-60.0 mcg/mL

**Clinical References:**
therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring,
ILAE Commission on Therapeutic Strategies. Epilepsia. 2008 Jul;49(7): 1239-1276

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**Fennel Seed, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE
antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and
clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of
sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and
wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease
and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to
identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm
sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity
of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with
the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
</tbody>
</table>
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.


FNTSX 62727

Fentanyl and Metabolite, Chain of Custody, Serum

Clinical Information: Fentanyl is an extremely fast acting synthetic opioid related to the phenylpiperidines.(1,2) It is available in injectable as well as transdermal formulations.(1) The analgesic effects of fentanyl is similar to those of morphine and other opioids (1); it interacts predominantly with the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissues.(1,3) Fentanyl is approximately 80% to 85% protein bound.(1) Fentanyl plasma protein binding capacity decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system. The average volume of distribution for fentanyl is 6 L/kg (range 3-8).(3,4) In humans, the drug appears to be metabolized primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug. Within 72 hours of intravenous (IV) administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with <10% representing unchanged drug.(3,4) The mean elimination half-life is: (1-3) - IV: 2 to 4 hours - Iontophoretic transdermal system (Ionsys), terminal half-life: 16 hours - Transdermal patch: 17 hours (range 103-22 hours, half-life is influenced by absorption rate) - Transmucosal: - Lozenge: 7 hours - Buccal tablet: 100 mcg to 200 mcg: 3 to 4 hours - 400 mcg to 800 mcg: 11 to 12 hours In clinical settings, fentanyl exerts its principal pharmacologic effects on the central nervous system. In additions to analgesia, alterations in mood, euphoria, dysphoria, and drowsiness commonly occur.(1,3) Because the biological effects of fentanyl are similar to those of heroin and other opioids, fentanyl has become a popular drug of abuse. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

Useful For: Monitoring fentanyl therapy Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: Both fentanyl and norfentanyl are reported. Tolerant individuals may require many-fold increases in dose to achieve the same level of analgesia, which can greatly complicate interpretation of therapeutic drug monitoring (TDMA) results and establishment of a therapeutic window. Concentration at which toxicity occurs varies and should be interpreted in light of clinical situation.

Reference Values:
Not applicable

**Fentanyl Screen with Reflex, Urine**

**Clinical Information:** This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (i.e., unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive rate due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also has a false-negative rate to the antibody’s ability to cross-react with different drugs in the class being screened for.

**Useful For:** Screening for drug abuse or use involving fentanyl

**Interpretation:** This assay only provides a preliminary analytical test result. A more specific alternative method (i.e., liquid chromatography-tandem mass spectrometry: LC-MS/MS) must be used to obtain a confirmed analytical result.

**Reference Values:**
- Negative
  - Screening cutoff concentration:
    - Fentanyl: 2 ng/mL

**Clinical References:**

**Fentanyl Screen, Urine**

**Clinical Information:** This procedure uses immunoassay reagents that are designed to produce a negative result when no drugs are present in a natural (i.e., unadulterated) specimen of urine; the assay is designed to have a high true-negative rate. Like all immunoassays, it can have a false-positive rate due to cross-reactivity with natural chemicals and drugs other than those they were designed to detect. The immunoassay also has a false-negative rate to the antibody’s ability to cross-react with different drugs in the class being screened for.

**Useful For:** Screening for drug abuse or use involving fentanyl

**Interpretation:** This assay only provides a preliminary analytical test result. A more specific alternative method (i.e., liquid chromatography-tandem mass spectrometry: LC-MS/MS) must be used to obtain a confirmed analytical result.

**Reference Values:**
- Negative
  - Screening cutoff concentration:
    - Fentanyl: 2 ng/mL

**Clinical References:**

**Fentanyl with Metabolite Confirmation, Chain of Custody, Urine**

**Clinical Information:** Fentanyl is an extremely fast acting synthetic opioid related to the phenylpiperidines.(1,2) It is available in injectable as well as transdermal formulations.(1) The analgesic effects of fentanyl is similar to those of morphine and other opioids(1): it interacts predominantly with
the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal
cord, and other tissue.(1,3) Fentanyl is approximately 80% to 85% protein bound. In plasma, the protein
binding capacity of fentanyl decreases with increasing ionization of the drug. Alterations in pH may
affect its distribution between plasma and the central nervous system (CNS). The average volume of
distribution for fentanyl is 6 L/kg (range 3-8).(3,4) In humans, the drug appears to be metabolized
primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not
contribute materially to the observed activity of the drug. Within 72 hours of intravenous (IV)
administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with <10%
representing unchanged drug.(3,4) The mean elimination half-life is (1-3): -IV: 2 to 4 hours
-Iontophoretic transdermal system (Ionsys) terminal half-life: 16 hours -Transdermal patch: 17 hours
(13-22 hours, half-life is influenced by absorption rate) -Transmucosal: -Lozenge: 7 hours -Buccal
tablet -100 mcg to 200 mcg: 3 to 4 hours -400 mcg to 800 mcg: 11 to 12 hours In clinical settings,
fentanyl exerts its principal pharmacologic effects on the CNS. In addition to analgesia, alterations in
mood (euphoria, dysphoria) and drowsiness commonly occur.(1,3) Because the biological effects of
fentanyl are similar to those of heroin and other opioids, fentanyl has become a popular drug of abuse.

Chain of custody is a record of the disposition of a specimen to document who collected it, who handled
it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be
performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection and confirmation of illicit drug use involving fentanyl Chain of custody is
required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights
of the individual contributing the specimen by demonstrating that it was under the control of personnel
involved with testing the specimen at all times; this control implies that the opportunity for specimen
tampering would be limited.

**Interpretation:** The presence of fentanyl >0.20 ng/mL or norfentanyl >1.0 ng/mL is a strong indicator
that the patient has used fentanyl.

**Reference Values:**

Negative

Cutoff concentrations:

- Immunoassay screen
- <2 ng/mL

Fentanyl by LC-MS/MS
- 0.2 ng/mL

Norfentanyl by LC-MS/MS
- 1.0 ng/mL

**Clinical References:**
for fentanyl is 6 L/kg (range 3-8).(3,4) In humans, the drug appears to be metabolized primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug. Within 72 hours of intravenous (IV) administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with <10% representing unchanged drug.(3,4) The mean elimination half-life is (1-3): -IV: 2 to 4 hours -Iontophoretic transdermal system (Ionsys) terminal half-life: 16 hours -Transdermal patch: 17 hours (13-22 hours, half-life is influenced by absorption rate) -Transmucosal:  - Lozenge: 7 hours - Buccal tablet - 100 to 200 mcg: 3 to 4 hours - 400 to 800 mcg: 11 to 12 hours In clinical settings, fentanyl exerts its principal pharmacologic effects on the CNS. In addition to analgesia, alterations in mood (euphoria, dysphoria) and drowsiness commonly occur.(1,3) Because the biological effects of fentanyl are similar to those of heroin and other opioids, fentanyl has become a popular drug of abuse.

Useful For: Detection and confirmation of illicit drug use involving fentanyl

Interpretation: The presence of fentanyl >0.20 ng/mL or norfentanyl >1.0 ng/mL is a strong indicator that the patient has used fentanyl.

Reference Values: Negative


Fentanyl, Serum

Clinical Information: Fentanyl is an extremely fast acting synthetic opioid related to the phenylpiperidines.(1,2) It is available in injectable as well as transdermal formulations.(1) The analgesic effects of fentanyl is similar to those of morphine and other opioids(1): it interacts predominantly with the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissues.(1,3) Fentanyl is approximately 80% to 85% protein bound.(1) Fentanyl plasma protein binding capacity decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system. The average volume of distribution for fentanyl is 6 L/kg (range 3-8).(3,4) In humans, the drug appears to be metabolized primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug. Within 72 hours of intravenous (IV) administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with less than 10% representing unchanged drug.(3,4) The mean elimination half-life is (1-3): -IV: 2 to 4 hours -Iontophoretic transdermal system (Ionsys) terminal half-life: 16 hours -Transdermal patch: 17 hours (13-22 hours, half-life is influenced by absorption rate) -Transmucosal:  - Lozenge: 7 hours - Buccal tablet - 100 to 200 mcg: 3 to 4 hours - 400 to 800 mcg: 11 to 12 hours In clinical settings, fentanyl exerts its principal pharmacologic effects on the CNS. In addition to analgesia, alterations in mood (euphoria, dysphoria) and drowsiness commonly occur.(1,3) Because the biological effects of fentanyl are similar to those of heroin and other opioids, fentanyl has become a popular drug of abuse.

Useful For: Monitoring fentanyl therapy

Interpretation: Both fentanyl and norfentanyl are reported. Tolerant individuals may require many-fold increases in dose to achieve the same level of analgesia, which can greatly complicate interpretation of therapeutic drug monitoring (TDMA) results and establishment of a therapeutic window. Concentration at which toxicity occurs varies and should be interpreted in light of clinical situation.

Reference Values: Not applicable

**FEEP**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
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</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**FERR**

**Clinical Information:** Ferritin is a large spherical protein consisting of 24 noncovalently linked...
subunits with a molecular weight of approximately 450,000 daltons. The subunits form a shell surrounding a central core containing variable amounts of ferric hydroxyphosphate. One molecule of ferritin is capable of binding between 4,000 and 5,000 atoms of iron, making ferritin the major iron storage protein for the body. Ferritin is found chiefly in the cytoplasm of cells of the reticuloendothelial system and is a constituent of normal human serum. The concentration of ferritin is directly proportional to the total iron stores in the body, resulting in serum ferritin concentrations becoming a common diagnostic tool in the evaluation of iron status. In most normal adults, serum ferritin concentrations vary with age and sex. There is a sharp rise in serum ferritin concentrations in the first month of life, coinciding with the depression of bone marrow erythropoiesis. Within 2 or 3 months, erythropoiesis becomes reactivated and there is a drop in the concentration of serum ferritin. By 6 months, the concentration is reduced to fairly low levels where they remain throughout childhood. There is no sex difference until the onset of puberty, at which time ferritin concentrations rise, particularly in males. There is a significant positive correlation between age and serum ferritin concentrations in females, but not in males. Patients with iron deficiency anemia have serum ferritin concentration approximately one-tenth of normal subjects, while patients with iron overload (hemochromatosis, hemosiderosis) have serum ferritin concentrations much higher than normal. Studies also suggest that serum ferritin provides a sensitive means of detecting iron deficiency at an early stage. Serum ferritin concentrations may serve as a tool to monitor the effects of iron therapy, but results should be interpreted with caution, as these cases may not always reflect the true state of iron stores. Ferritin is a positive acute phase reactant in both adults and children, whereby chronic inflammation results in a disproportionate increase in ferritin in relation to iron reserves. Elevated ferritin is also observed in acute and chronic liver disease, chronic renal failure, and in some types of neoplastic disease. Evaluating body iron stores may include serum iron determination, total iron binding capacity (TIBC), and percent saturation of transferrin, however are subject to diurnal variations and may be less precise. Additionally, they do not discriminate between depleted iron stores (iron deficiency) and conditions associated with defective iron release (eg, anemia of chronic disease).

**Useful For:** Aiding in the diagnosis of iron deficiency and iron overload conditions Differentiating iron deficiency anemia and anemia of chronic disease

**Interpretation:** Hypoferritinemia is associated with increased risk for developing iron deficiency where iron deficiency is sufficient to reduce erythropoiesis causing hemoglobin concentrations to fall. Latent iron deficiency occurs when serum ferritin is low without low hemoglobin. Hyperferritinemia is associated with iron overload conditions including hereditary hemochromatosis where concentrations may exceed 1,000 mcg/L. Non-iron overload hyperferritinemia may be caused by common liver disorders, neoplasms, acute or chronic inflammation, and hereditary hyperferritinemia-cataract syndrome. For more information about hereditary hemochromatosis testing, see Hereditary Hemochromatosis Algorithm in Special Instructions.

**Reference Values:**
- Males: 24-336 mcg/L
- Females: 11-307 mcg/L

**Clinical References:**

**Ferrochelatase (FECH) Gene, Full Gene Analysis**

**Clinical Information:** Erythropoietic protoporphyria (EPP) is an inherited disorder of porphyrin metabolism whose clinical manifestations include painful photodermatosis without blisters and liver disease. The disorder results from decreased activity of the enzyme ferrochelatase (FECH). FECH is the last of 8 enzymes acting sequentially in the heme biosynthetic pathway and is encoded by the FECH gene located on chromosome 18. The skin symptoms in EPP include immediate painful photosensitivity, usually beginning in early infancy upon sun exposure. Repeated photosensitivity episodes result in skin thickening and areas of hyperkeratosis. This is typically noted on areas where sun exposure is most common, such as the dorsa of the hands and on the face. A small number of patients with EPP develop liver complications. Hepatic disease in EPP may include cholelithiasis and chronic
liver disease progressing to rapid acute liver failure. Biochemically, EPP is characterized by elevated protoporphyrin levels in red blood cells, which fluorescence under Wood's light due to the accumulation of free protoporphyrin IX. Protoporphyrin elevations may also be found in plasma and stool, but not in all patients. Urine protoporphyrin levels are usually normal unless there is liver involvement. Studies have also suggested that a reduction in activity of ferrochelatase to <50% of normal levels can induce clinical manifestations. The gold standard test for the diagnosis of EPP is biochemical analysis (PEE / Porphyrins Evaluation, Whole Blood), interpreted in the context of clinical features. In most patients with EPP, a pathogenic FECH mutation that reduces enzyme activity by 50% can be identified on only 1 allele. Clinical expression of EPP typically requires a hypomorphic (low expression) FECH allele (IVS3-48T->C) in trans (on a different chromosome) with the mutation. IVS3-48T->C is a variant of the FECH gene associated with reduced gene expression. This variant is found in approximately 10% of the general Caucasian population. Autosomal recessive inheritance (2 pathogenic mutations in trans) is infrequent, accounting for <4% of EPP cases. In contrast to patients with 1 pathogenic mutation and the low-expression allele, missense mutations are far more common than null mutations. It is uncertain whether protoporphyric liver failure is more common among individuals with a single null (splicing defect, nonsense, or frameshift) mutation than those with 2 pathogenic mutations as some literature has suggested. In any case, it is certain that all EPP patients should be monitored for hepatic disease and actively manage their photosensitivity.

**Useful For:** Confirmation of a diagnosis of erythropoietic protoporphyria (EPP) following positive biochemical genetic test results obtained through PEE / Porphyrins Evaluation, Whole Blood Carrier testing for individuals with a family history of EPP in the absence of known mutations in the family

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Fetomaternal Bleed, Flow Cytometry, Blood**

**Clinical Information:** In hemolytic disease of the newborn, fetal red cells become coated with IgG alloantibody of maternal origin, directed against an antigen on the fetal cells that is of paternal origin and absent on maternal cells. The IgG-coated cells undergo accelerated destruction, both before and after birth. The clinical severity of the disease can vary from intrauterine death to hematological abnormalities detected only if blood from an apparently healthy infant is subject to serologic testing. Pregnancy causes immunization when fetal red cells possessing a paternal antigen foreign to the mother enter the maternal circulation, an event described as fetomaternal hemorrhage (FMH). FMH occurs in up to 75% of pregnancies, usually during the third trimester and immediately after delivery. Delivery is the most common immunizing event, but fetal red cells can also enter the mother's circulation after amniocentesis, spontaneous or induced abortion, chorionic villus sampling, cordocentesis, or rupture of an ectopic pregnancy, as well as blunt trauma to the abdomen.(1) Rh immune globulin (RhIG, anti-D antibody) is given to Rh-negative mothers who are pregnant with an Rh-positive fetus. Anti-D antibody binds to fetal D-positive red cells, preventing development of the maternal immune response. RhIG can be given either before or after delivery. The volume of FMH determines the dose of RhIG to be administered.
**Useful For:** Determining the volume of fetal-to-maternal hemorrhage for the purposes of recommending an increased dose of the Rh immune globulin

**Interpretation:** Greater than 15 mL of fetal red blood cells (RBC) (30 mL of fetal whole blood) is consistent with significant fetomaternal hemorrhage (FMH). A recommended dose of Rh immune globulin (RhIG) will be reported for all specimens. One 300 mcg dose of RhIG protects against a FMH of 30 mL of D-positive fetal whole blood or 15 mL of D-positive fetal RBCs. Recommended standard of practice is to administer RhIG within 72 hours of the fetomaternal bleed for optimal protective effects. The effectiveness of RhIG decreases beyond 72 hours post exposure but may still be clinically warranted. This assay has been validated out to 5 days post collection.

**Reference Values:**
< or = 1.5 mL of fetal RBCs in normal adults


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**FMBNY**

**Fetomaternal Bleed, New York**

**Clinical Information:** In hemolytic disease of the newborn, fetal red cells become coated with IgG alloantibody of maternal origin, directed against an antigen on the fetal cells that is of paternal origin and absent on maternal cells. The IgG-coated cells undergo accelerated destruction, both before and after birth. The clinical severity of the disease can vary from intrauterine death to hematological abnormalities detected only if blood from an apparently healthy infant is subject to serologic testing. Pregnancy causes immunization when fetal red cells possessing a paternal antigen foreign to the mother enter the maternal circulation, an event described as fetomaternal hemorrhage (FMH). FMH occurs in up to 75% of pregnancies, usually during the third trimester and immediately after delivery. Delivery is the most common immunizing event, but fetal red cells can also enter the mother's circulation after amniocentesis, spontaneous or induced abortion, chorionic villus sampling, cordocentesis, or rupture of an ectopic pregnancy, as well as blunt trauma to the abdomen. Rh immune globulin (RhIG, anti-D antibody) is given to Rh-negative mothers who are pregnant with an Rh-positive fetus. Anti-D antibody binds to fetal D-positive red cells, preventing development of the maternal immune response. RhIG can be given either before or after delivery. The volume of FMH determines the dose of RhIG to be administered.

**Useful For:** Determining the volume of fetal-to-maternal hemorrhage for the purposes of recommending an increased dose of the Rh immune globulin. This is only for specimens collected in New York state.

**Interpretation:** Greater than 15 mL of fetal red blood cells (RBC) (30 mL of fetal whole blood) is consistent with significant fetomaternal hemorrhage (FMH). A recommended dose of Rh immune globulin (RhIG) will be reported for all specimens. One 300-mcg dose of RhIG protects against a FMH of 30 mL of D-positive fetal whole blood or 15 mL of D-positive fetal RBCs. Recommended standard of practice is to administer RhIG within 72 hours of the fetomaternal bleed for optimal protective effects. The effectiveness of RhIG decreases beyond 72 hours post exposure but may still be clinically warranted. This assay has been validated out to 5 days postcollection.

**Reference Values:**
< or = 1.5 mL of fetal RBCs in normal adults

**FGF1**

**FGFR1 (8p11.2) Amplification, FISH, Tissue**

**Clinical Information:** Fibroblast growth factor receptor 1 (FGFR1) is a receptor tyrosine kinase. FGFR1 overexpression or amplification in squamous cell carcinoma is associated with tumor growth. Studies have shown overexpression or amplification of FGFR1 to be vulnerable to FGFR-tyrosine kinase inhibitors and FGFR1 inhibitors maybe a promising therapeutic option and have shown tumors with FGFR1 amplification may be sensitive to FGFR1 tyrosine kinase inhibitors.

**Useful For:** Providing prognostic information and guiding treatment primarily for patients with squamous cell carcinoma of the lung, breast, esophagus, thymus, and other locations

**Interpretation:** FGFR1 will be clinically interpreted as positive or negative. The FGFR1 locus is reported as amplified when the FGFR1:D8Z2 ratio is >2.0 or an average of 6 or more copies of the FGFR1 locus are observed per tumor nucleus. A tumor with an FGFR1:D8Z2 ratio ≤2.0 and having an average of <6 copies of FGFR1 per tumor nucleus is considered negative for amplification of the FGFR1 locus.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FGFRF**

**FGFR1 (8p11.2) Rearrangement, FISH**

**Clinical Information:** The gene for fibroblast growth factor receptor 1 (FGFR1) is located at 8p11.2 and rearrangements of FGFR1 are found in stem cell myeloproliferative disorders involving both lymphoid and myeloid lineages. The stem cell myeloproliferative disorders with FGFR1 rearrangements are also called 8p11 (eight p11) myeloproliferative syndromes (EMS) and have variable presentations. EMS often transform rapidly into myelomonocytic leukemia and generally have a poor outcome due to resistance to current chemotherapies, including imatinib myesylate; median survival is about 12 months. All translocations affecting FGFR1 have a similar structure with a 5' gene partner translocating to the 3' FGFR1 at exon 9. The fusion transcripts encode large proteins containing the N-terminus of the translocation partner, and the tyrosine kinase domain of FGFR1 in the C-terminus. Leukemogenesis is caused by inappropriate activation of FGFR1.

**Useful For:** An aid in identifying patients with myeloproliferative syndromes and the t(8;var)(p11.2;var) translocation who therefore are likely resistant to current chemotherapies

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for any given probe. The presence of a positive clone supports a diagnosis of malignancy. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
FGFR2

**FGFR2 (10q26.1) Rearrangement, FISH, Tissue**

**Clinical Information:** Cholangiocarcinoma is a malignancy arising from the biliary tract epithelium. These tumors are often clinically advanced at the time of presentation and the prognosis is very poor with a short overall survival. Treatment is generally limited to surgical resection, which is associated with a high degree of morbidity, and palliative chemotherapy regimens. Therefore, additional treatment options are eagerly sought. Rearrangement of the FGFR2 gene region has been identified in a subset of cholangiocarcinomas. These rearrangements result in overexpression of FGFR2, which offers the possibility of using targeted FGFR2-inhibitor therapy for treatment. FGFR2 rearrangement has been identified in a number of other cancers including those of the bladder, thyroid, oral cavity, and brain. In the future, it is likely that the presence of FGFR2 rearrangements will be exploited in the treatment of these cancers as well.

**Useful For:** Providing prognostic information and guiding treatment for patients with cholangiocarcinomas and other tumor types including bladder, thyroid, oral cavity, and brain

**Interpretation:** A positive result is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result suggests rearrangement of the FGFR2 locus and a tumor that may be responsive to targeted FGFR2-inhibitor therapy. A negative result suggests no rearrangement of the FGFR2 gene region at 10q26.1.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

MSFGN

**Fibrillary Glomerulonephritis Confirmation, Paraffin, LC-MS/MS**

**Clinical Information:** Fibrillary glomerulonephritis (FGN) is a rare kidney disease with fibrillary deposits in the glomeruli that contain polyclonal IgG and complement, indicating immune complex deposition. Although usually Congo-red negative, more recently cases with weak Congo-red positivity have been observed, making the distinction from amyloid more challenging. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) performed on microdissected glomeruli from patients with FGN demonstrate a unique proteomic profile including the protein DNAJB9 (Mayo Clinic unpublished observations). The presence of DNAJB9 was found to be highly sensitive and specific for FGN, distinguishing it from other glomerular diseases including amyloid, immunotactoid glomerulopathy, and immune complex-mediated proliferative glomerulonephritis. The presence of DNAJB9, in the appropriate clinical and pathological context, can be useful to establish a diagnosis of FGN.

**Useful For:** Diagnosis of fibrillary glomerulonephritis

**Interpretation:** An interpretation will be provided.

FGAZ

Fibrinogen Alpha-Chain (FGA) Gene, Full Gene Analysis

Clinical Information: The systemic amyloidoses are a number of disorders of varying etiology characterized by extracellular protein deposition. The most common form is an acquired amyloidosis secondary to multiple myeloma or monoclonal gammopathy of unknown significance (MGUS) in which the amyloid is composed of immunoglobulin light chains. In addition to light chain amyloidosis, there are a number of acquired amyloidoses caused by the misfolding and precipitation of a wide variety of proteins. There are also hereditary forms of amyloidosis. The hereditary amyloidoses comprise a group of autosomal dominant, late-onset diseases that show variable penetrance. A number of genes have been associated with hereditary forms of amyloidosis including those that encode transthyretin, apolipoprotein A1, apolipoprotein AII, gelsolin, cystatin C, lysozyme, and fibrinogen alpha chain (FGA). Apolipoprotein A1, apolipoprotein AII, lysozyme, and fibrinogen amyloidosis present as nonneuropathic systemic amyloidosis, with renal dysfunction being the most prevalent manifestation. FGA-related familial visceral amyloidosis commonly presents with renal failure, which can often be fulminant, and is characterized by hypertension, proteinuria, and azotemia. Liver and spleen involvement may be seen in advanced cases. Neuropathy is not a feature of FGA-related familial visceral amyloidosis. Due to the clinical overlap between the acquired and hereditary forms, it is imperative to determine the specific type of amyloidosis in order to provide an accurate prognosis and consider appropriate therapeutic interventions. Tissue-based, laser-capture tandem mass spectrometry might serve as a useful test preceding gene sequencing to better characterize the etiology of the amyloidosis, particularly in cases that are not clinically clear. It is important to note that there are rare disorders of hemostasis that are also associated with mutations in the FGA gene. Patients with afibrinogenemia, hypofibrinogenemia, and dysfibrinogenemia have all been reported to have mutations in FGA. Most dysfibrinogenemias are autosomal dominant disorders; afibrinogenemia and hypofibrinogenemia are more often autosomal recessive disorders. In general, truncating mutations in FGA result in afibrinogenemia and missense mutations are a common cause of dysfibrinogenemia.

Useful For: Confirming a diagnosis of fibrinogen alpha-chain (FGA) gene-related familial visceral amyloidosis

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.

**FIBAG**

### Fibrinogen Antigen, Plasma

**Clinical Information:** Fibrinogen (clotting factor I) is an essential protein responsible for blood clot formation. In the final step of the coagulation cascade, thrombin converts soluble fibrinogen into insoluble fibrin strands that crosslink and form a clot. Fibrinogen is synthesized in the liver and has a biological half-life of 3 to 5 days in the circulating plasma. Fibrinogen deficiencies can be congenital or acquired and lead to prolonged coagulation times. Isolated fibrinogen deficiency is an extremely rare inherited coagulation disorder. Acquired fibrinogen deficiency is most commonly caused by, acute or decompensated intravascular coagulation and fibrinolysis (DIC). Other causes of fibrinogen deficiency include advanced liver disease, L-asparaginase therapy, or fibrinolytic agents (eg, streptokinase, urokinase, tissue plasminogen activator).

**Useful For:** Evaluation of fibrinogen deficiency Measuring fibrinogen in patients with elevated plasma levels of fibrin degradation products, patients receiving heparin, and in patients with antibodies to thrombin (following surgical use of topical bovine thrombin) Identifying afibrinogenemia, hypofibrinogenemia and dysfibrinogenemia when ordered in combination with fibrinogen activity (FIB / Fibrinogen,Plasma)

**Interpretation:** This method measures the total amount of fibrinogen protein (ie, fibrinogen antigen) present in the plasma. Adequate fibrinogen antigen levels in a context of low fibrinogen activity suggests a dysfibrinogenemia. Fibrinogen antigen levels <100 mg/dL are associated with an increased risk of bleeding.

**Reference Values:**
196-441 mg/dL


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**FIBTP**

### Fibrinogen, Plasma

**Clinical Information:** Fibrinogen, also known as factor I, is a plasma protein that can be transformed by thrombin into a fibrin gel (“the clot”). Fibrinogen is synthesized in the liver and circulates in the plasma as a disulfide-bonded dimer of 3 subunit chains. The biological half-life of plasma fibrinogen is 3 to 5 days. An isolated deficiency of fibrinogen may be inherited as an autosomal recessive trait (afibrinogenemia or hypofibrinogenemia) and is one of the rarest of the inherited coagulation factor deficiencies. Acquired causes of decreased fibrinogen levels include: acute or decompensated intravascular coagulation and fibrinolysis (disseminated intravascular coagulation: DIC), advanced liver disease, L-asparaginase therapy, and therapy with fibrinolytic agents (eg, streptokinase, urokinase, tissue plasminogen activator). Fibrinogen function abnormalities, dysfibrinogenemias, may be inherited (congenital) or acquired. Patients with dysfibrinogenemia are generally asymptomatic. However, the congenital dysfibrinogenemias are more likely than the acquired to be associated with bleeding or thrombotic disorders. While the dysfibrinogenemias are generally not associated with clinically significant hemostasis problems, they characteristically produce a prolonged thrombin time clotting test. Acquired dysfibrinogenemias mainly occur in association with liver disease (eg, chronic hepatitis, hepatoma) or renal diseases (eg, chronic glomerulonephritis, hypernephroma) and usually are associated with elevated fibrinogen levels. Fibrinogen is an acute phase reactant, so a number of acquired conditions can result in an increase in its plasma concentration: -Acute or chronic inflammatory illnesses -Nephrotic syndrome -Liver disease and cirrhosis -Pregnancy or estrogen therapy -Compensated intravascular coagulation -Diabetes -Obesity The finding of an increased level of fibrinogen in a patient with obscure symptoms suggests an organic rather than a functional condition. Chronically increased fibrinogen has been recognized as a risk factor for development of arterial thromboembolism.
Useful For: Detecting increased or decreased fibrinogen (factor I) concentration of acquired or congenital origin. Monitoring severity and treatment of disseminated intravascular coagulation and fibrinolysis.

Interpretation: Fibrinogen may be decreased in acquired conditions such as liver disease and acute intravascular coagulation and fibrinolysis and disseminated intravascular coagulation (ICF/DIC). Fibrinogen may be decreased in rare conditions including congenital afibrinogenemia or hypofibrinogenemia. Fibrinogen may be elevated with acute or chronic inflammatory conditions.

Reference Values:
200-393 mg/dL


FIBR
8482

Fibroblast Culture
Clinical Information: Cultures of skin fibroblasts are useful for specialized testing, which requires skin cells. These cells can be cultured and tested at Mayo Clinic or sent to external laboratories performing these specialized tests. In addition, cells are frozen for at least 3 years for potential future studies on cultured cells or for molecular genetic testing.

Useful For: A preliminary step in obtaining cultured cells for specialized testing including enzymatic and molecular genetic

Reference Values: Not applicable

Clinical References:

CULFB
35257

Fibroblast Culture for Genetic Testing
Clinical Information: Fibroblast cells may be used to perform a wide range of laboratory tests. Prior to testing, the tissue may need to be cultured to obtain adequate numbers of cells.

Useful For: Producing fibroblast cultures that can be used for genetic analysis. Once confluent flasks are established, the fibroblast cultures are sent to other laboratories, either within Mayo Clinic or to external sites, based on the specific testing requested.

FGF23
88662

Fibroblast Growth Factor 23 (FGF23), Plasma
Clinical Information: Fibroblast growth factor 23 (FGF23) is a major regulator of phosphate homeostasis. It may act in concert with several other less well-characterized phosphate regulators. FGF23 is secreted primarily by bone, followed by thymus, heart, brain and, in low levels, by several other tissues. It is coexpressed with the X-linked phosphate-regulating endopeptidase (PHEX). High serum phosphate levels stimulate FGF23 expression and secretion through as yet poorly understood mechanisms. PHEX appears to modulate this process, possibly in part through cleavage of FGF23. Only intact FGF23 is considered bioactive. It interacts with a specific receptor on renal tubular cells, decreasing expression of type IIa sodium/phosphate cotransporters, resulting in decreased phosphate reabsorption. In addition, gene transcription of 1-a-hydroxylase is downregulated, reducing bioactive 1,25-dihydroxy vitamin D (1,25-2OH-VitD), thereby further decreasing phosphate reabsorption. Eventually, falling serum phosphate levels lead to diminished FGF23 secretion, closing the feedback loop. Measurement of FGF23 can assist in diagnosis and management of disorders of phosphate and bone metabolism in patients with either normal or impaired renal function. When FGF23 levels are pathologically elevated in individuals with normal renal function, hypophosphatemia, with or without osteomalacia, ensues. This can occur with rare, usually benign, mixed connective tissue tumors that contain characteristic complex vascular structures,
osteoclast-like giant cells, cartilaginous elements, and dystrophic calcifications. These neoplasms secrete FGF23 ectopically and autonomously (oncogenic osteomalacia). In less than one-fourth of cases a different benign or malignant, soft tissue tumor type, or, extremely rarely, a carcinoma, may be the cause of paraneoplastic FGF23 secretion. In either scenario, complete removal of the tumor cures the oncogenic osteomalacia. Hypophosphatemia and skeletal abnormalities are also observed in X-linked hypophosphatemia (XLH) and autosomal dominant hypophosphatemic rickets (ADHR). In XLH, mutations of PHEX reduce its negative modulatory effect on bioactive FGF23 secretion. In ADHR, FGF23 mutations render it resistant to proteolytic cleavage, thereby increasing FGF23 levels. However, not all FGF23 mutations increase renal phosphate secretions. Mutations that impair FGF23 signaling, rather than increase its protease resistance, are associated with the syndrome of familial tumoral calcinosis (ectopic calcifications) with hyperphosphatemia. In patients with renal failure, FGF23 contributes to renal osteodystrophy. The patient's kidneys can no longer excrete sufficient amounts of phosphate. This leads to marked increases in FGF23 secretions in a futile compensatory response, aggravating the 1,25-2OH-VitD deficiency of renal failure and the consequent secondary hyperparathyroidism.

**Useful For:** Diagnosing and monitoring oncogenic osteomalacia Possible localization of occult neoplasms causing oncogenic osteomalacia Diagnosing X-linked hypophosphatemia or autosomal dominant hypophosphatemic rickets Diagnosing familial tumoral calcinosis with hyperphosphatemia Predicting treatment response to calcitriol or vitamin D analogs in patients with renal failure

**Interpretation:** The majority of patients with oncogenic osteomalacia have fibroblast growth factor 23 (FGF23) levels >2 times the upper limit of the reference interval. However, since the condition is a rare cause of osteomalacia, a full baseline biochemical osteomalacia workup should precede FGF23 testing. This should include measurements of the serum concentrations of calcium, magnesium, phosphate, alkaline phosphate, creatinine, parathyroid hormone (PTH), 25-hydroxy vitamin D (25-OH-VitD), 1,25-2OH-VitD, and 24-hour urine excretion of calcium and phosphate. Findings suggestive of oncogenic osteomalacia, which should trigger serum FGF23 measurements, are a combination of normal serum calcium, magnesium, and PTH; normal or near normal serum 25-OH-VitD; low or low-normal serum 1,25-2OH-VitD; low-to-profoundly low serum phosphate; and high urinary phosphate excretion. Once oncogenic osteomalacia has been diagnosed, the causative tumor should be sought and removed. Complete removal can be documented by normalization of serum FGF23 levels. Depending on the magnitude of the initial elevation, this should occur within a few hours to a few days (half-life of FGF23 is approximately 20 to 40 minutes). Persistent elevations indicate incomplete removal of tumor. Serial FGF23 measurements during follow-up may be useful for early detection of tumor recurrence, or in partially cured patients, as an indicator of disease progression. Because FGF23 has a short half-life, selective venous sampling with FGF23 measurements may be helpful in localizing occult tumors in patients with oncogenic osteomalacia. However, the most useful diagnostic cutoff for gradients between systemic and local levels has yet to be established. X-linked hypophosphatemia (XLH) and most cases of autosomal dominant hypophosphatemic rickets (ADHR) present before the age of 5 as vitamin D-resistant rickets. FGF23 is significantly elevated in the majority of cases. Genetic testing provides the exact diagnosis. A minority of patients with ADHR may present later, as older children, teenagers, or young adults. These patients may have clinical features and biochemical findings, including FGF23 elevations, indistinguishable from oncogenic osteomalacia patients. Genetic testing may be necessary to establish a definitive diagnosis. Patients with familial tumoral calcinosis and hyperphosphatemia have loss-of-function FGF23 mutations. The majority of these FGF23 mutant proteins are detected by FGF23 assays. The detected circulating levels are very high, in a futile compensatory response to the hyperphosphatemia. Almost all patients with renal failure have elevated FGF23 levels, and FGF23 levels are inversely related to the likelihood of successful therapy with calcitriol or active vitamin D analogs. Definitive cutoffs remain to be established, but it appears that renal failure patients with FGF23 levels of >50 times the upper limit of the reference range have a low chance of a successful response to vitamin D analogues (<5% response rate).

**Reference Values:**
Results may be significantly elevated (ie, >900 RU/mL) in normal infants <3 months of age.
- 3 months-17 years: < or =230 RU/mL
- > or =18 years: < or =180 RU/mL

**Clinical References:** 1. Online Mendelian Inheritance of Man (OMIM) entry *605380 Fibroblast Growth Factor 23; FGF23, Retrieved 1/25/06, Available from URL:

FGFRC 71483

Fibroblast Growth Factor Receptor 1 (FGFR1) IHC, Technical Component Only

Clinical Information: FGFR1 is a receptor tyrosine kinase that belongs to the fibroblast growth factor family. FGFR1 amplification is seen in 13% to 22% of lung squamous cell carcinoma (SQCC) and has been associated with a worse prognosis. For instance, FGFR1 expression in head and neck SQCC correlates with poor histologic differentiation, wide invasion, and abundant nuclear pleomorphism. Anti-FGFR inhibitors are now in early clinical trials and have shown to inhibit growth and induce apoptosis in lung cancer cell lines.

Useful For: Classification of a subset of lung squamous cell carcinoma

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


PRKAF 64777

Fibrolamellar Carcinoma, 19p13.1 (PRKACA) Rearrangement, FISH, Tissue

Clinical Information: DNAJB1-PRKACA fusion has been associated with a distinct subtype of hepatocellular carcinoma called fibrolamellar carcinoma. A break-apart strategy FISH probe has been developed to detect the rearrangement event that occurs in the DNAJB1-PRKACA fusion, specifically the loss of the 5' region labeled in red and retention of the 3' region labeled in green.

Useful For: Aid in the diagnosis of identifying PRKACA gene rearrangements of patients with fibrolamellar carcinoma

Interpretation: A positive result with the PRKACA probe is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result of PRKACA suggests fusion of the PRKACA and DNAJB1 genes at 19p13.1. A negative result suggests no fusion of the PRKACA and DNAJB1 genes has occurred.

Reference Values:
An interpretive report will be provided.

FibroTest-ActiTest, Serum

Clinical Information: Fibrosis and inflammatory activity are the 2 main causes of liver disease. FibroTest-ActiTest estimates the levels of fibrosis and cirrhosis in the liver as well as the level of necroinflammatory activity. The estimation is made by measuring 6 standard serum biomarkers (gamma-glutamyl transferase, total bilirubin, alpha-2-macroglobulin, apolipoprotein A1, haptoglobin, and alanine aminotransferase). The activity score is a measure of liver inflammation caused by disease. Results from these tests are combined with the patient’s age and sex to estimate hepatic fibrosis and inflammatory activity scores. Hepatic fibrosis is typically compared to a form of scar tissue that progresses throughout the liver. The most serious stage of fibrosis is known as cirrhosis.

Useful For: Evaluating hepatic fibrosis in chronic hepatitis C patients, Diagnosing fibrosis in carriers of chronic hepatitis B virus, Evaluating hepatic fibrosis in co-infected HIV carriers, Providing access to new-generation noninterferon treatment for hepatitis, Evaluating fibrosis in patients suffering from metabolic conditions (nonalcoholic fatty liver disease) and patients who consume excess alcohol.

Interpretation: FibroTest-ActiTest provides a score that assesses hepatic fibrosis (F0-F4) and a score that assesses hepatic inflammatory activity (A0-A3). Interpretation of the score is provided in the report. Individual results from the 6 component tests are also provided with institution-specific reference intervals. Fibrosis is reported relative to a scale ranging from F0-F4 (F0=no fibrosis, F1=minimal fibrosis, F2=moderate fibrosis, F3=advanced fibrosis, F4=severe fibrosis). Fibrosis scores may overlap (eg, F0/F1, F1/F2). Activity is reported relative to a scale ranging from A0-A3 (A0=no activity, A1=minimal activity, A2=significant activity, A3=severe activity). Activity scores may overlap (eg, A0/A1, A1/A2).

Reference Values:

<table>
<thead>
<tr>
<th>FibroTest Score</th>
<th>Stage</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00-0.21*</td>
<td>F0</td>
<td>No fibrosis</td>
</tr>
<tr>
<td>0.21-0.27*</td>
<td>F0-F1</td>
<td>No fibrosis</td>
</tr>
<tr>
<td>0.27-0.31*</td>
<td>F1</td>
<td>Minimal fibrosis</td>
</tr>
<tr>
<td>0.31-0.48*</td>
<td>F1-F2</td>
<td>Minimal fibrosis</td>
</tr>
<tr>
<td>0.48-0.58*</td>
<td>F2</td>
<td>Moderate fibrosis</td>
</tr>
<tr>
<td>0.58-0.72*</td>
<td>F3</td>
<td>Advanced fibrosis</td>
</tr>
<tr>
<td>0.72-0.74*</td>
<td>F3-F4</td>
<td>Advanced fibrosis</td>
</tr>
<tr>
<td>0.74-1.00</td>
<td>F4</td>
<td>Severe fibrosis (Cirrhosis)</td>
</tr>
</tbody>
</table>

*Boundary values can apply to 2 stages based on rounding. For example, a FibroTest score of 0.305 will round up to 0.31 and be staged F1. A FibroTest score of 0.314 will round down to 0.31 and be staged F1-F2.

<table>
<thead>
<tr>
<th>ActiTest Score</th>
<th>Grade</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00-0.17*</td>
<td>A0</td>
<td>No activity</td>
</tr>
<tr>
<td>0.17-0.29*</td>
<td>A0-A1</td>
<td>No activity</td>
</tr>
<tr>
<td>0.29-0.36*</td>
<td>A1</td>
<td>Minimal activity</td>
</tr>
<tr>
<td>0.36-0.52*</td>
<td>A1-A2</td>
<td>Minimal activity</td>
</tr>
<tr>
<td>0.52-0.60*</td>
<td>A2</td>
<td>Significant activity</td>
</tr>
</tbody>
</table>
0.60-0.62* A2-A3 Significant activity
0.62-0.100 A3 Severe activity *Boundary values can apply to 2 grades based on rounding. For example, an ActiTest score of 0.285 will round up to 0.29 and be graded A0-A1. An ActiTest score of 0.294 will round down to 0.29 and be graded A1.

ALPHA-2-MACROGLOBULIN 100-280 mg/dL

ALANINEAMINOTRANSFERASE (ALT) Males: No established reference values > or =1 year: 7-55 U/L Females: No established reference values > or =1 year: 7-45 U/L

APOLIPOPROTEIN A1 Males: No established reference values 2-17 years: Low: Borderline low: 115-120 mg/dL Acceptable: >120 mg/dL > or =18 years: > or =120 mg/dL Females: No established reference values 2-17 years: Low: Borderline low: 115-120 mg/dL Acceptable: >120 mg/dL > or =18 years: > or =140 mg/dL

GAMMA-GLUTAMYLTRANSFERASE (GGT) Males: 0-11 months: 12 months-6 years: 7-12 years: 13-17 years: or =18 years: 8-61 U/L Females: 0-11 months: 12 months-6 years: 7-12 years: 13-17 years: or =18 years: 5-36 U/L

HAPTOGLOBIN 30-200 mg/dL

BILIRUBIN, TOTAL 0-6 days: Refer to www.bilitool.org for information on age-specific (postnatal hour of life) serum bilirubin values. 7-14 days: 15 days to 17 years: < or =1.0 mg/dL > or =18 years: < or =1.2 mg/dL

**Clinical References:**

**FIGE**

**Fig (Ficus carica) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal/Borderline 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 High Positive 4 17.50 â€“ 49.99 Very High Positive 5 50.00 â€“ 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**
<0.35 kU/L

**FFAG4**

**Filaria IgG4 Antibody, ELISA**

**Reference Values:**
Reference Range: <1:50

**Interpretive Criteria:**
<1:50 Negative
1.50-3.00 Equivocal
>3.00 Positive
This assay detects Filaria IgG4 associated with infections caused by the major filarial parasites, including Dirofilaria immitis, Wuchereria bancrofti, Brugia malayi, and Onchocerca volvulus. Detection of IgG4 subclass antibody offers enhanced specificity without sacrifice of sensitivity. Chronic filarial infections manifesting as elephantiasis may not show a significant IgG4 response, and cannot be ruled out by this assay. Equivocal results may represent cross-reactive antibodies induced by infection with other nematodes.

**Filaria, Blood**

**Clinical Information:** The filariae are parasitic nematodes (roundworms) that cause significant human morbidity in tropical regions worldwide. The macroscopic adults live in the human host and release microscopic offspring (microfilariae) into the blood or skin. The microfilariae of Wuchereria bancrofti, Brugia malayi, B timori, Loa loa, Mansonella perstans, and M ozzardi are found in the blood, while the microfilariae of Onchocerca volvulus and M streptocerca are found in the skin. If microfilariae are taken up by a biting insect vector (mosquitos, blackflies, midges, and deer flies), they undergo further development in the insect and can then be transmitted to other humans. W bancrofti and the Brugia species cause a serious condition called lymphatic filariasis. The adults live in the lymphatics and cause inflammation and scarring of the lymph vessels. Over time, the lymphatic channels are obstructed and fluid cannot drain back to the heart, resulting in massive lymphedema (elephantiasis) of the affected limb or groin. W bancrofti is found in the tropics worldwide, while Brugia species are found in parts of Asia and Southeast Asia. Loa loa causes migratory subcutaneous angioedema referred to as "calabar swellings" as the adult worm migrates throughout the body. The adult occasionally migrates across the surface of the eye, giving it the moniker "the African eye worm." Loa loa is only found in Africa. Finally, M perstans and M ozzardi cause a relatively mild form of filariasis. Patients are often asymptomatic. When present, symptoms include fever, angioedema, headache, myalgias, arthralgias, pruritus, and neurologic manifestations. M perstans is found in parts of Africa and South America, while M ozzardi is only found in Mexico and Central and South America. The microfilariae of these filarial worms can be seen on conventional thick and thin blood films, which allows for their definitive identification. However, microfilariae may be in low numbers and, therefore, use of concentration methods such as the Knott's technique improves the detection sensitivity. Some microfilariae are released into the blood at certain times of the day; W bancrofti and Brugia species are usually released between 10 p.m. and 2 a.m. (nocturnal periodicity), while L loa is released mostly from 10 a.m. and 2 p.m. (diurnal periodicity). It is therefore important to collect blood during these time periods for optimal detection sensitivity. Mansonella species microfilariae do not exhibit any periodicity and, therefore, a random blood draw is acceptable. Since the levels of parasitemia may fluctuate, multiple smears may be needed to detect the filarial worms. Blood should be obtained and examined every 8 to 12 hours for 2 to 3 days before excluding infection.

**Useful For:** Detection of microfilariae in peripheral blood

**Interpretation:** Positive results are provided with the genus and species of the microfilariae, if identifiable.

**Reference Values:**

Negative

If positive, organism is identified.

**Clinical References:** Centers for Disease Control and Prevention, Division of Parasitic Diseases and Malaria. DPDx, Diagnostic Procedures. 2013. Available at http://www.cdc.gov/dpdx/diagnosticProcedures/blood/specimencoll.html

**Finch Feathers, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Firebush (Kochia), IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
</tbody>
</table>

1STT 87857

First Trimester Maternal Screen

Clinical Information: Multiple marker serum screening has become a standard tool used in obstetric care to identify pregnancies that may have an increased risk for certain birth defects such as Down syndrome and trisomy 18. Second-trimester multiple marker screening has been well established for over a decade. During 2002 through 2006, first-trimester screening has been established as an alternative option of equal or better performance compared with the best second-trimester screening programs. The first-trimester screen is performed by measuring analytes in maternal serum that are produced by the fetus and the placenta. Additionally, the nuchal translucency (NT) measurement is a sonographic marker shown to be effective in screening fetuses for Down syndrome. A mathematical model is used to calculate a risk estimate by combining the analyte values, NT measurement, and maternal demographic information. The laboratory establishes a specific cutoff for each condition, which classifies each screen as either screen-positive or screen-negative. A screen-positive result indicates that the value obtained exceeds the established cutoff. A positive screen does not provide a diagnosis, but indicates that further evaluation should be considered. Serum Analytes Human chorionic gonadotropin (total beta-hCG): hCG is a glycoprotein consisting of alpha and beta subunits. hCG is synthesized by placental cells starting very early in pregnancy and serves to maintain the corpus luteum and, hence, progesterone production during the first trimester. Thereafter, the concentration of hCG begins to fall as the placenta begins to produce steroid hormones and the role of the corpus luteum in maintaining pregnancy diminishes. Increased total hCG levels are associated with an increased risk for Down syndrome. Pregnancy-associated plasma protein A (PAPP-A): PAPP-A is a 187 kDa protein comprised of 4 subunits: 2 PAPP-A subunits and 2 pro-major basic protein (proMBP) subunits. PAPP-A is a metalloproteinase that cleaves insulin-like growth factor-binding protein-4 (IGFBP-4), dramatically reducing IGFBP-4 affinity for IGF1 and IGF2, thereby regulating the availablity of these growth factors at the tissue level. PAPP-A is highly expressed in first-trimester trophoblasts, participating in regulation of fetal growth. Levels in maternal serum increase throughout pregnancy. Low PAPP-A levels before the 14th week of gestation are associated with an increased risk for Down syndrome and trisomy 18. Nuchal translucency (NT): The NT measurement, an ultrasound marker, is obtained by measuring the fluid-filled space within the nuchal region (back of the neck) of the fetus. While fetal NT measurements obtained by ultrasonography increase in normal pregnancies with advancing gestational age, Down syndrome fetuses have larger NT measurements than gestational age-matched normal fetuses. Increased fetal NT measurements can therefore serve as an indicator of an increased risk for Down syndrome.


Interpretation: Screen-Negative: A screen-negative result indicates that the calculated screen risk is below the established cutoff of 1/230 for Down syndrome and 1/100 for trisomy 18. A negative screen does not guarantee the absence of trisomy 18 or Down syndrome. Screen-negative results typically do not warrant further evaluation. Screen-Positive: When a Down syndrome risk cutoff of 1/230 is used for follow-up, the combination of maternal age, pregnancy-associated plasma protein A, human chorionic gonadotropin, and nuchal translucency has an overall detection rate of approximately 85% with a false-positive rate of 5% to 10%. In practice, both the detection rate and false-positive rate increase with age, thus detection and positive rates will vary depending on the age distribution of the screening population.
Reference Values:

DOWN SYNDROME
Calculated screen risks <1/230 are reported as screen negative.
Risks > or =1/230 are reported as screen positive.

TRISOMY 18
Calculated screen risks <1/100 are reported as screen negative.
Risks > or =1/100 are reported as screen positive. A numeric risk for trisomy 18 risk is provided with positive results on non-diabetic, non-twin pregnancies.

An interpretive report will be provided.


**Fish and Shellfish Panel IgG**

Reference Values:
Clam IgG
Codfish/Scrod IgG
Crab IgG
Lobster IgG
Oyster IgG
Red Snapper IgG
Salmon IgG
Sardine/Pilchard IgG
Shrimp IgG
Sole IgG
Trout IgG
Tuna IgG

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicated immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Flecainide, Serum**

Clinical Information: Flecainide (Tambocor) is a class I cardiac antiarrhythmic agent with electrophysiologic properties similar to lidocaine, quinidine, procainamide, and tocainide. Flecainide produces a dose-related decrease in intracardiac conduction in all parts of the heart, with the greatest
effect on the His-Purkinje system. Atrial effects are limited. Flecainide causes a dose-related and plasma concentration-related decrease in single and multiple premature ventricular contractions and can suppress recurrence of ventricular tachycardia. Flecainide is eliminated from blood by hepatic metabolism as well as renal clearance; significant changes in either organ system will cause impaired clearance. During preclinical trials, patients with congestive heart failure were observed to have radically altered clearance properties. Cardiac toxicity attributed to flecainide is related to its cardiac conduction slowing properties. Excessive prolongation of PR, QRS, and QT intervals occurs with increased amplitude of the T wave. Reductions in myocardial rate, contractility, as well as conduction disturbances, are also associated with excessive dose and plasma concentration of flecainide. Death can occur from hypotension, respiratory failure, and asystole. Flecainide is contraindicated in patients with sick sinus syndrome. It causes sinus bradycardia, sinus pause, or sinus arrest.

Useful For: Optimizing dosage Assessing toxicity Monitoring compliance

Interpretation: Flecainide is most effective in premature ventricular contractions suppression at plasma concentrations in the range of 0.2 to 1.0 mcg/mL. Plasma concentrations >1.0 mcg/mL are associated with a high rate of cardiac adverse experiences such as conduction defects or bradycardia. Therapeutic concentration: 0.2 to 1.0 mcg/mL. Toxic concentration: >1.0 mcg/mL

Reference Values:
0.2-1.0 mcg/mL


FLG
Gene, Mutation Analysis

Clinical Information: Ichthyosis vulgaris is a common disease with an incidence rate of approximately 1 in 250. It is characterized by palmar hyperlinearity, keratosis pilaris, xerosis, and prominent fine scaling of the extensor surfaces of the extremities, the scalp, central part of the face, and the trunk. The clinical onset typically occurs within the first few years of life. Approximately 37% to 50% of people with ichthyosis vulgaris have atopic diseases and about 8% of patients with atopic diseases have classic features of ichthyosis vulgaris. A large number of epidemiological studies support an increased risk and severity of asthma that occurs in association with atopic disease. Clinical presentation associated with ichthyosis vulgaris can be confirmed by genetic testing. Ichthyosis vulgaris is caused by loss-of-function alterations in the filaggrin (FLG) gene on chromosome 1q21. Filaggrin is a filament aggregating protein that promotes terminal differentiation of the epidermis and skin barrier formation. This prevents epidermal water loss and inhibits entry of allergens, toxic chemicals, and infectious organisms. Loss of filaggrin expression causes cytoskeletal disorganization leading to clinical phenotype associated with ichthyosis vulgaris. FLG mutations are found in about 7.7% of Europeans and 3% of Asians. However, these mutations appear to be less common in dark-skinned ethnicities. The R501X and 2282del4 are complete loss-of-function mutations accounting for approximately 80% of mutations in the Northern European population. However, they are rarer in the Southern European population. These 2 alterations have been shown to be very strong predisposing factors for atopic diseases. FLG mutations in other ethnicities are different than those found in European-origin populations. This disease is inherited in a semidominant manner (ie, heterozygotes have either no symptoms or milder ichthyosis vulgaris and homozygotes/compound heterozygotes show marked ichthyosis vulgaris).

Useful For: Genetic diagnosis of ichthyosis vulgaris for clinical management, risk assessment for atopic diseases and atopic disease-associated asthma, and genetic counseling for family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
Interpretive report will be provided.


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**FLI1**

**FLI-1 Immunostain, Technical Component Only**

**Clinical Information:** Friend leukemia virus integration 1 (FLI1) is a member of the erythroblast transformation specific (ETS) family of transcription factors. It has antiapoptotic activity and also interferes with nuclear hormone receptor signaling. A chromosomal translocation between the FLI1 gene and the EWS gene is found in most Ewing sarcomas. In normal tissues, nuclear staining for FLI1 is seen in endothelial cells, a subset of T cells, megakaryocytes, and normal breast epithelium. Studies have shown FLI1 expression in endothelial-derived tumors, Ewing sarcoma, Merkel cell carcinoma, lung adenocarcinoma, melanoma, and erythroleukemia, and lack of expression in rhabdomyosarcoma, desmoplastic round cell tumors, and colon adenocarcinoma.

**Useful For:** Aids in phenotyping endothelial-derived tumors, Ewing sarcoma, Merkel cell carcinoma, lung adenocarcinoma, melanoma, and erythroleukemia

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**FLNDR**

**Flounder (Bothidae/Pleuronectidae Fam) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal/Borderline 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 High Positive 4 17.50 â€“ 49.99 Very High Positive 5 50.00 â€“ 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:** <0.35 kU/L
FLT3 Mutation Analysis, Varies

Clinical Information: The FMS-like tyrosine gene (FLT3) codes for a transmembrane receptor/signaling protein (FLT3) of the tyrosine kinase group. Binding of FLT3 ligand to the FLT3 receptor ultimately leads to production of proteins that cause cell growth and inhibit cell death through apoptosis. Recently, mutations in FLT3 have been found in some hematopoietic neoplasms, and are particularly common in adult acute myeloid leukemia (AML) with an overall incidence of approximately 20% to 30%. The highest mutation rates are seen in adult patients with AML and normal- or intermediate-risk cytogenetics, and patients with acute promyelocytic leukemia. The most common FLT3 mutation consists of internal tandem duplication (ITD) of DNA sequences found in exons 14 or 15. In some subgroups of adults with AML, the presence of an FLT3 ITD mutation has been found to be an adverse prognostic indicator. The second most common mutation is a point mutation in the codon for an aspartate residue (D835) that resides in the activation loop of the FLT3 protein. D835 mutations have been identified in approximately 7% of AML cases but, at this time, it is not clear if the presence of this mutation has any prognostic significance. It is thought that both types of FLT3 mutations lead to constitutive (always present, independent of internal or external stimuli) FLT3 activation. Identification of an FLT3 mutation in AML is clinically useful not only because of the prognostic information it provides, but also because FLT3-inhibitory drugs have shown promise as useful therapeutic agents.

Useful For: A prognostic indicator in some acute myeloid leukemia patients

Interpretation: An interpretive report will be issued indicating whether the FLT3 internal tandem duplication or D835 mutation, or both, were detected. Mutation status will be indicated as positive or negative. If internal tandem duplication (ITD) positive, an allelic ratio will be reported.

Reference Values:
An interpretive report will be provided.


Flunitrazepam Confirmation, Serum

Reference Values:
Units: Flunitrazepam ng/mL 7-Aminoflunitrazepam ng/mL

Peak plasma Flunitrazepam concentrations in patients receiving chronic, recommended dosages: 10 â€“ 20 ng/mL.

Note: Flunitrazepam is not legally marketed in the United States.

Fluoride, Plasma

Clinical Information: Fluoride induces bone formation by stimulating osteoblasts. Because fluorides increase bone density, they are used in dental preparations and as an antosteoporotic agent. However, prolonged high exposure to fluoride produces changes in bone morphology consistent with osteomalacia, including prolonged mineralization lag time and increased osteoid thickness. The adverse skeletal effects of fluoride are associated with plasma fluoride >4 mcmol/L. Chronic fluorosis may produce osteosclerosis, periostitis, calcification of ligaments and tendons, and crippling deformities. Prolonged exposure to the fluoride-containing antifungal agent voriconazole can produce high plasma fluoride concentrations and bone changes (periostitis).

Useful For: Assessing accidental fluoride ingestion Monitoring patients receiving sodium fluoride for bone disease or patients receiving voriconazole therapy

Interpretation: Humans exposed to fluoride-treated water typically have plasma fluoride in the range
of 1 to 4 mcmol/L. Those who are not drinking fluoride-treated water have plasma fluoride <1 mcmol/L. Plasma fluoride values >4 mcmol/L indicate excessive exposure and are associated with periostitis.

Reference Values:
0.0-4.0 mcmol/L


Fluoxetine, Serum

Clinical Information: Fluoxetine is a selective serotonin reuptake inhibitor approved for treatment of bulimia, obsessive-compulsive behavior, panic, premenstrual dysphoria, and major depressive disorder, with a variety of off-label uses. Both fluoxetine and its major metabolite, norfluoxetine, are pharmacologically active, and are reported together in this assay. Most individuals respond optimally when combined serum concentrations for both parent and metabolite are in the therapeutic range (120-300 ng/mL) at steady state. Due to the long half-lives of parent and metabolite (1-6 days), it may take several weeks for patients to reach steady-state concentrations. Fluoxetine is a potent inhibitor of the metabolic enzyme CYP2D6, with lesser inhibitory effects on CYP2C19 and CYP3A. Therapy with fluoxetine is therefore subject to numerous drug interactions, which is compounded by wide interindividual variability in fluoxetine pharmacokinetics. Measurement of the drug is useful for managing comedinations, dose or formulation changes, and in assessing compliance. Side effects are milder for fluoxetine than for older antidepressants such as the tricyclics. The most common side effects of fluoxetine therapy include nausea, nervousness, anxiety, insomnia, and drowsiness. Anticholinergic and cardiovascular side effects are markedly reduced compared to tricyclic antidepressants. Fatalities from fluoxetine overdose are extremely rare.

Useful For: Monitoring serum concentration of fluoxetine during therapy Evaluating potential toxicity Evaluating patient compliance

Interpretation: Most individuals display optimal response to fluoxetine when combined serum levels of fluoxetine and norfluoxetine are between 120 and 300 ng/mL. Some individuals may respond well outside of this range, or may display toxicity within the therapeutic range, thus interpretation should include clinical evaluation. A toxic range has not been well established.

Reference Values:
Fluoxetine + norfluoxetine: 120-300 ng/mL


Fluphenazine (Prolixin), Serum

Reference Values:
Reference Range: 1.0 - 10 ng/mL

Flurazepam (Dalmene) and Desalkylflurazepam

Reference Values:
Flurazepam:
Fluticasone 17-Beta-Carboxylic Acid, Urine

Clinical Information: Inhaled corticosteroids are the single most effective therapy for adult patients with asthma. Even low doses of inhaled corticosteroids have been shown to reduce mortality related to asthma. The September 2007 issue of Pediatrics reported that "Verification of (asthma) treatment adherence by objective measures remains necessary."(1) In this pediatric asthma adherence study, the 104 asthmatic children and their parents grossly overestimated their medication adherence. Over 1 of 3 responses reported full compliance to medications when no medications had been taken. Over 46% of individuals exaggerated their adherence by at least 25%. The authors concluded that "Under the best of conditions in this study, accuracy of self-report was insufficient to provide a stand-alone measure of adherence."(1,2) Fluticasone propionate (FP) is an inhaled corticosteroid with anti-inflammatory and immunosuppressive properties commonly used for the treatment of asthma, airway inflammation, and allergic rhinitis. FP is typically well tolerated and has a low risk for adverse systemic effects when utilized at recommended therapeutic doses. However, noncompliance with recommended FP therapy may result in poorly controlled asthma or misinterpretation of the patient's therapeutic responsiveness. Patients with excessive exposure to FP may present with clinical features of Cushing syndrome, but with evidence of hypothalamic-pituitary-adrenal axis suppression, including suppressed cortisol levels. Conversely, a patient not administering the drug as recommended may have their therapeutic responsiveness interpreted, in error by the patient or clinician, as steroid-resistance. FP has low oral bioavailability and high hepatic first-pass metabolism, which results in low plasma FP concentrations; any systemic levels are believed to occur through adsorption from the lungs. Native FP absorbed by the gastrointestinal tract (<1% total FP) is rapidly metabolized by cytochrome P450 isoform 3A4 to yield fluticasone 17-beta-carboxylic acid, its primary metabolic product.(3) Fluticasone 17-beta-carboxylic acid is pharmacologically inactive and has increased water solubility such that it is excreted in urine. Accordingly, fluticasone 17-beta-carboxylic acid is detected in urine in individuals recently exposed to inhaled FP therapy. Fluticasone 17-beta-carboxylic acid may be detected in urine as early as 16 to 24 hours following a patient's first administration of low dose (220 mcg) FP therapy. The window of detection for fluticasone 17-beta-carboxylic acid is 6 days following cessation of FP therapy.

Useful For: Assessing compliance (recent exposure) to fluticasone propionate therapy An aid in the evaluation of secondary adrenal insufficiency

Interpretation: Elevated fluticasone 17-beta-carboxylic acid indicates recent exposure to fluticasone propionate (FP). Fluticasone 17-beta carboxylic acid concentration <10 pg/mL indicates that the patient may not have administered inhaled FP therapy within the preceding 6 days. Validated concerns about suboptimal patient adherence to asthma controller medications should lead to patient and provider interactions to address potential compliance issues.

Reference Values:
Negative
   Cutoff concentration: 10 pg/mL

Values for normal patients not taking fluticasone propionate should be less than the cutoff concentration (detection limit).


**FFVOX**  
57731  
**Fluvoxamine (Luvox)**  
**Reference Values:**  
Units: ng/mL

Expected fluvoxamine concentrations on recommended daily dosage regimens:  
50-900 ng/mL

**IAPC**  
113345  
**FNA Immediate Adequacy (Bill Only)**  
**Reference Values:**  
This test is for billing purposes only.  
This is not an orderable test.

**IAAPC**  
113346  
**FNA Immediate Adequacy Add'l (Bill Only)**  
**Reference Values:**  
This test is for billing purposes only.  
This is not an orderable test.

**PGXFP**  
65566  
**Focused Pharmacogenomics Panel**  

**Useful For:** Preemptive or reactive genotyping of patients for pharmacogenomic purposes Providing an assessment for genes with strong drug-gene associations

**Interpretation:** An interpretive report will be provided that focuses on only drugs and genes with published pharmacogenomic practice guidance by the Clinical Pharmacogenetics Implementation Consortium, other professional organizations or where strong FDA guidance has been issued in drug labels. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.
Reference Values:
An interpretive report will be provided.


FOL
9198

Folate, Serum

Clinical Information: The term folate refers to all derivatives of folic acid. For practical purposes, serum folate is almost entirely in the form of N-(5)-methyl tetrahydrofolate.(1) Approximately 20% of the folate absorbed daily is derived from dietary sources; the remainder is synthesized by intestinal microorganisms. Serum folate levels typically fall within a few days after dietary folate intake is reduced and may be low in the presence of normal tissue stores. RBC folate levels are less subject to short-term dietary changes. Significant folate deficiency is characteristically associated with macrocytosis and megaloblastic anemia. Lower than normal serum folate also has been reported in patients with neuropsychiatric disorders, in pregnant women whose fetuses have neural tube defects, and in women who have recently had spontaneous abortions.(2) Folate deficiency is most commonly due to insufficient dietary intake and is most frequently encountered in pregnant women or in alcoholics. Other causes of low serum folate concentration include: -Excessive utilization (eg, liver disease, hemolytic disorders, and malignancies) -Rare inborn errors of metabolism (eg, dihydrofolate reductase deficiency, formiminotransferase deficiency, 5,10-methylenetetrahydrofolate reductase deficiency, and tetrahydrofolate methyltransferase deficiency)

Useful For: Investigation of suspected folate deficiency

Interpretation: Serum folate is a relatively nonspecific test.(3) Low serum folate levels may be seen in the absence of deficiency and normal levels may be seen in patients with macrocytic anemia, dementia, neuropsychiatric disorders, and pregnancy disorders. Results <4 mcg/L are suggestive of folate deficiency. The cutoff is based on consensus and was derived from the US NHANES III data.(4) Evaluation of macrocytic anemias commonly requires measurement of the serum concentration of both vitamin B12 and folate; ideally they should be measured at the same point in time. Serum folate measurement is preferred over RBC folate measurement due to considerable analytic variability (coefficient of variation: CV) of assays. Both results give the same interpretation (internal Mayo study) therefore RBC folate quantitation is not recommended. Additional serum testing with homocysteine and methylmalonic acid (MMA) determinations may help distinguish between vitamin B12 and folate deficiency states. In folate deficiency, homocysteine levels are elevated and MMA levels are normal. In vitamin B12 deficiency, the analytic variability (CV) of both serum and RBC folate assays is considerable. Homocysteine and MMA levels are alternate determinates of folate deficiency. See Vitamin B12 Deficiency Evaluation in Special Instructions.

Reference Values:
> or =4.0 mcg/L
<4.0 mcg/L suggests folate deficiency

**Follicle Stimulating Hormone, Beta Subunit (Beta FSH) Immunostain, Technical Component Only**

**Clinical Information:** Follicle stimulating hormone (FSH) stimulates maturation of ovarian follicles and estrogen secretion in females. Sparse population of cells stain positively in normal pituitary gland (approximately 10% of cells). This population of gonadotrophs also produces luteinizing hormone. Immunohistochemical detection of beta FSH (bFSH) may be useful in the classification of pituitary adenomas.

**Useful For:** Classification of pituitary adenomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**Follicle-Stimulating Hormone, Serum**

**Clinical Information:** Luteinizing hormone (LH) is a glycoprotein hormone consisting of 2 noncovalently bound subunits (alpha and beta). Gonadotropin-releasing hormone from the hypothalamus controls the secretion of the gonadotropins, follicle-stimulating hormone (FSH), and LH from the anterior pituitary. The menstrual cycle is divided by a midcycle surge of both FSH and LH into a follicular phase and a luteal phase. FSH appears to control gametogenesis in both males and females.

**Useful For:** An adjunct in the evaluation of menstrual irregularities Evaluating patients with suspected hypogonadism Predicting ovulation Evaluating infertility Diagnosing pituitary disorders

**Interpretation:** In both males and females, primary hypogonadism results in an elevation of basal follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. FSH and LH are generally elevated in:
- Primary gonadal failure
- Complete testicular feminization syndrome
- Precocious puberty (either idiopathic or secondary to a central nervous system lesion)
- Menopause (postmenopausal FSH levels are generally >40 IU/L)
- Primary ovarian hypofunction in females
- Primary hypogonadism in males

Normal or decreased FSH in:
- Polycystic ovary disease in females
- FSH and LH are both decreased in failure of the pituitary or hypothalamus.

**Reference Values:**
Males
- <12 months: < or =3.3 IU/L
- ≥12 months-< or =5 years: < or =1.9 IU/L
- >5 years-< or =10 years: < or =2.3 IU/L
- ≥10 years-< or =15 years: 0.6-6.9 IU/L
- ≥15 years-< or =18 years: 0.7-9.6 IU/L
>18 years: 1.2-15.8 IU/L

TANNER STAGES*
Stage I: <1.5 IU/L
Stage II: <3.0 IU/L
Stage III: 0.4-6.2 IU/L
Stage IV: 0.6-5.1 IU/L
Stage V: 0.8-7.2 IU/L

*Puberty onset occurs for boys at a median age of 11.5 (+/- 2) years. For boys there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.

Females
<12 months: 1.2-12.5 IU/L
> or = 12 months - < or = 10 years: 0.5-6.0 IU/L
>10 years - < or = 15 years: 0.9-8.9 IU/L
>15 years - < or = 18 years: 0.7-9.6 IU/L

Premenopausal:
Follicular: 2.9-14.6 IU/L
Midcycle: 4.7-23.2 IU/L
Luteal: 1.4-8.9 IU/L
Postmenopausal: 16.0-157.0 IU/L

TANNER STAGES*
Stage I: 0.6-4.1 IU/L
Stage II: 0.3-5.8 IU/L
Stage III: 0.1-7.2 IU/L
Stage IV: 0.3-7.0 IU/L
Stage V: 0.4-8.6 IU/L
*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/- 2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html


FOOD6 Food Panel

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Food Panel #2**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
**Reference Values:**

Class IgE kU/L  Interpretation

0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.


**FFPG4**

**Food Panel IgG4 (532)**

**Reference Values:**

- Corn IgG
- Egg White IgG
- Egg Yolk IgG
- Milk Cow IgG
- Peanut IgG
- Soybean IgG
- Wheat IgG
- Yeast (Saccharomyces cerevisiae) IgG

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization to the food allergen in question.

**FFPII**

**Food Panel II IgG**

**Reference Values:**

- Barley IgG  <2.0
- Beef IgG  <2.0
- Casein IgG  <2.0
- Chicken IgG  <2.0
- Chocolate/Cacao IgG  <2.0
- Codfish/Scrod IgG  <2.0
- Corn IgG  <2.0
Egg White IgG <2.0
Malt IgG <2.0
Oat IgG <2.0
Orange IgG <2.0
Peanut IgG <2.0
Pork IgG <2.0
Potato White IgG <2.0
Rye Food IgG <2.0
Soybean IgG <2.0
Tomato IgG <2.0
Wheat IgG <2.0
Yeast (Saccharomyces cerevisiae) IgG <2.0

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**FOOD2**

**Food-Fruit Panel**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<td>2</td>
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<td>3</td>
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<td>4</td>
<td>17.5-49.9</td>
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Current as of October 11, 2018 2:20 pm CDT   800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com

Food-Grain Panel

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>6</td>
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Reference values apply to all ages.


Food-Nut Panel # 1

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>Strongly positive Reference values apply to all ages.</td>
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sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


**FOOD7 81875 Food-Seafood Panel**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
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</tr>
<tr>
<td>1</td>
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Food-Vegetable Panel

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.

Formaldehyde, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
</tbody>
</table>

Reference values apply to all ages.


Formic Acid, Serum/Plasma

Reference Values:

Reporting limit determined each analysis

Normal: Average 5 mcg/mL (range 0-12)

Formic acid is a metabolite of Formaldehyde and an index of exposure to Formaldehyde and (other) precursors.
**Formic Acid, Urine**

**Reference Values:**
Reporting limit determined each analysis

Creatinine (mg/L)
U.S. Population (10th - 90th percentiles, median)
All participants:
335 - 2370 mg/L, median: 1180 (n=22,245)
Males:
495 - 2540 mg/L, median: 1370 (n=10,610)
Females:
273 - 2170 mg/L, median 994 (n=11,635)

Formic Acid (mcg/mL)
Synonym(s): Formate

Normal 95% population range: 5 - 36 mcg/mL urine.

Formic Acid (Creatinine Corrected) (mg/g Creat)
Synonym(s): Formate

Specific Gravity Confirmation
Physiologic range: 1.010 - 1.030

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**FOXL2 Mutation Analysis, Tumor**

**Clinical Information:** Granulosa cell tumor (GCT) represents approximately 5% to 10% of all ovarian malignancies and is the most common type of malignant ovarian sex-cord stromal tumor. The majority of patients with GCT (95%) are adults and 5% are juveniles. The histopathological diagnosis of GCT is challenging. Forkhead box L2 (FOXL2) gene is involved in ovarian development and function. The FOXL2 gene point mutation 402C->G in exon 1 (C134W) was reported in the majority of adult GCT (>90%), 5% to 10% of thecomas (tumors closely related to GCT) and less than 10% of juvenile GCT cases, but not in other ovarian tumors. Detection of FOXL2 mutation aids in the clinical diagnosis of adult GCT. Next-generation sequencing has recently emerged as an accurate, cost-effective method to identify alterations across numerous genes. This test uses formalin-fixed paraffin-embedded tissue or cytology slides to assess for common somatic mutations in the FOXL2 gene known to be associated with adult GCT. The results of this test can be useful for supporting a diagnosis of adult GCT.

**Useful For:** Assisting in the clinical diagnosis of adult granulosa cell tumor (GCT) by assessing gene targets with in the FOXL2 gene

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

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**FOXP1**

Current as of October 11, 2018 2:20 pm CDT
800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
**FOXP1 Immunostain, Technical Component Only**

**Clinical Information:** FOXP1 is a member of the forkhead box family of transcription factors that have a variety of functions in different cell and tissue types. Gene expression profiling and immunophenotypic studies showed that FOXP1 is expressed in normal activated B cells and overexpressed in a subset of diffuse large B-cell lymphomas (DLBCL) with a predominantly nongerminall center phenotype.

**Useful For:** Classification of lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**FOXP3 Immunostain, Technical Component Only**

**Clinical Information:** FOXP3 is a transcription factor implicated in T-cell regulation, activation, and differentiation. FOXP3 has been shown to be a master control gene for the development and function of CD4+/CD25+ regulatory T cells. In normal lymphoid tissues, a T-cell subset in interfollicular areas shows nuclear staining. FOXP3 is a specific marker for adult T-cell leukemia/lymphoma (ATLL).

**Useful For:** Classification of leukemias and lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

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Reference values apply to all ages.


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**Fragile X Syndrome, Molecular Analysis**

**Clinical Information:** Fragile X syndrome is an X-linked disorder with variable expression in males and females. It is caused by an expansion of the CGG trinucleotide repeat in the FMR1 gene, located on the X chromosome. This trinucleotide repeat is polymorphic in the general population, with the number of repeats ranging from 5 to 44. These normal alleles are passed from generation to generation with the number of repeats remaining constant. Small expansions, called premutations, most often range from 59 to 200 CGG repeats. Premutation carriers do not exhibit features of fragile X syndrome, but are at risk for other FMR1-related disorders such as fragile X tremor/ataxia syndrome (FXTAS) and premature ovarian failure (POF). Transmission of a premutation by a male to his daughter usually results in little or no change in the CGG repeat number. Transmission of a premutation by a female to her son or daughter usually results in further expansion, either to a larger premutation or a full mutation. The risk for a female premutation carrier to have a child affected with fragile X syndrome by expansion to a full mutation increases with the number of CGG repeats in the premutation. Full mutations can be 200 to thousands of repeats long, and are associated with abnormal methylation of a
region adjacent to the FMR1 gene. This is thought to interfere with normal FMR1 gene expression, resulting in fragile X syndrome. There are multiple clinical phenotypes associated with expansion (premutations and full mutations) in the FMR1 gene. Fragile X Syndrome: Approximately 1/4,000 individuals (male and female) are affected with fragile X syndrome. Most affected males exhibit moderate mental retardation, with affected females having milder (if any) cognitive deficiency. Neuropsychiatric diagnoses such as autism spectrum and anxiety disorders are common. Characteristic physical features include a long face with prominent jaw, protruding ears, connective tissue abnormalities, and large testicles in postpubertal males. Fragile X Tremor/Ataxia Syndrome (FXTAS): FXTAS is a neurodegenerative disorder that is clinically distinct from fragile X syndrome. Both male and female premutation carriers are at risk for FXTAS. However, the disorder is much less common, milder in presentation, and shows a later age of onset in females. Clinical hallmarks of the disorder include intention tremor, gait ataxia, dementia, and neuropsychiatric symptoms. The risk for FXTAS increases as the number of CGG repeats increases, and the majority of individuals with FXTAS have CGG repeat expansions of 70 or more. Penetration of clinical symptoms is associated with increasing age, with the majority of affected males showing symptoms between age 70 and 90. Premature Ovarian Failure (POF): Female premutation carriers are at risk for increased follicular stimulating hormone (FSH) levels, early menopause, and POF. Penetration and early onset of female reproductive symptoms correlates with increasing size of the CGG repeat, and reaches its highest penetrance at approximately 80 to 90 repeats. Of note, penetrance actually remains stable or may even decrease at approximately 100 repeats. There is no risk for increased penetrance of the POF phenotype due to maternal or paternal inheritance of the expanded CGG repeat.

Useful For: Determination of carrier status for individuals with a family history of fragile X syndrome or X-linked mental retardation Confirmation of a diagnosis of fragile X syndrome, fragile X tremor/ataxia syndrome, or premature ovarian failure caused by expansions in the FMR1 gene Prenatal diagnosis of fragile X syndrome when there is a documented FMR1 expansion in the family

Interpretation: An interpretive report will be provided.

Reference Values:
Normal alleles: 5-44 CGG repeats
Intermediate (grey zone) alleles: 45-54 CGG repeats
Premutation alleles: 55-200 CGG repeats
Full mutation alleles: >200 CGG repeats
An interpretive report will be provided.


FUFXS 35427 Fragile X, Follow up Analysis

Reference Values:
This is not an orderable test.

This follow-up test is added by the laboratory dependent upon on the result of the PCR analysis (FXS / Fragile X Syndrome, Molecular Analysis).

FRANC 91552 Francisellula Tularensis Antibody

Clinical Information: Tularemia antibody titers ≥ to 1:40 are of diagnostic significance. However, titers in this range may also indicate previous infection. Antibody begins to appear 2-3 week
post-onset and generally peaks at approximately 5 weeks into the disease. With this delay in antibody appearance a second specimen will usually demonstrate a diagnostic four-fold rise in titer for patients with active disease.

**Interpretation:** Interpretive Criteria: <1:20 Negative 1:20 - 1:80 Equivocal > or =1:160 Positive In the presence of compatible symptoms, a Francisella tularensis antibody titer of 1:160 or greater in an acute specimen supports a presumptive diagnosis of tularemia. However, a titer > or =1:160 may also reflect past infection. An equivocal titer may be due to cross-reactive antibodies (Brucella, Yersinia, or Proteus OX19), past infection, or very recent infection. A four-fold rise in titer between acute and convalescent sera is required for definitive serologic diagnosis of tularemia.

**Reference Values:**
Reference Range: <1:20

### NEFA

**Free Fatty Acids, Total, Serum**

**Clinical Information:** All but 2% to 5% of serum fatty acids are esterified. The "nonesterified" or "free" fatty acids are protein-bound. The amount of free fatty acids in the serum rises after a fatty meal, but tends to fall after ordinary meals. Levels are elevated in obesity. Lipoactive hormones such as epinephrine, norepinephrine, glucagon, thyrotropin, and adrenocorticotropic release free fatty acids. Tumors producing such hormones cause release of excessive quantities of free fatty acids. Serum free fatty acids are also increased in patients with uncontrolled type 2 diabetes mellitus and are an indicator of insulin resistance. Free fatty acids are associated with increased reactive oxygen species (ROS), probably mediated by free fatty acid activation of NADPH oxidase. The link between increased ROS and decreased nitric oxide production is a contributor to endothelial dysfunction.

**Useful For:** Evaluation of metabolic status of persons with endocrinopathies Detection of pheochromocytoma and of glucagon-, thyrotropin-, and adrenocorticotropic-secreting tumors Monitoring of control of diabetes mellitus (serum-free glycerol is a very useful companion test in assessing diabetes and may be ordered by special request from Mayo Medical Laboratories). The correlation with insulin resistance and downstream cardiovascular risk may be a useful treatment aid in some patients.

**Interpretation:** Abnormally high levels of free fatty acids are associated with uncontrolled diabetes mellitus and with conditions that involve excessive release of a lipoactive hormone such as epinephrine, norepinephrine, glucagon, thyrotropin, and adrenocorticotropic.

**Reference Values:**
> or =16 years: 0.00-0.72 mmol/L

Reference values have not been established for patients who are <16 years of age.


### FRTUP

**Free Thyroxine Index (FTI), Serum**

**Clinical Information:** The determination of the total thyroxine (T4) concentration is of importance in laboratory diagnostics for differentiating between euthyroid, hyperthyroid, and hypothyroid conditions. As the major fraction of the total thyroxine is bound to transport proteins (thyroxine-binding globulin: TBG, prealbumin, and albumin), the determination of total T4 only provides correct information when the thyroxine-binding capacity in serum is normal. The free thyroid hormones are in equilibrium with the hormones bound to the carrier proteins. The thyroid binding capacity or T-uptake assay provides a measure of the available thyroxine-binding sites. Determination of the free thyroxine index (FTI) from the quotient of total T4 and thyroxine-binding index (TBI) (TBI=result of the T-uptake determination) takes into account changes in the thyroid hormone carrier proteins and the thyroxine level. While total T4 is a relatively reliable indicator of T4 levels in the presence of normal...
binding proteins, it is not a reliable indicator when binding proteins are abnormal. For example, increases in thyroxine-binding proteins may cause increased total T4 levels despite normal free T4 levels and normal thyroid function. Results are changed by drugs or physical conditions that alter the patient's TBG levels, or drugs that compete with endogenous T4 and T3 for protein-binding sites. Direct measurement of free thyroxine (FRT4 / T4 [Thyroxine], Free, Serum by immunoassay) has replaced the FTI test in most clinical situations.

**Useful For:** Estimating the amount of circulating free thyroxine (free thyroxine index) using the total thyroxine and thyroid binding capacity (T-uptake)

**Interpretation:** The free thyroxine index (FTI) is determined by the following calculation: FTI = Thyroxine (T4)/Thyroid Binding Capacity The FTI is a normalized determination that remains relatively constant in healthy individuals and compensates for abnormal levels of binding proteins. Hyperthyroidism causes increased FTI and hypothyroidism causes decreased values.

**Reference Values:**

**Thyroxine Binding Capacity (units are in Thyroxine Binding Index: TBI):**
- 0-19 years: 0.8-1.2 TBI
- > or =20 years: 0.8-1.3 TBI

**T4 Total (T4):**
- 0-5 days: 5.0-18.5 mcg/dL
- 6 days-2 months: 5.4-17.0 mcg/dL
- 3-11 months: 5.7-16.0 mcg/dL
- 1-5 years: 6.0-14.7 mcg/dL
- 6-10 years: 6.0-13.8 mcg/dL
- 11-19 years: 5.9-13.2 mcg/dL
- > or =20 years: 4.5-11.7 mcg/dL

**Free Thyroxine Index:**
- 0-5 days: 5.1-20.8 mcg/dL
- 6 days-2 months: 5.5-18.0 mcg/dL
- 3-11 months: 5.7-16.8 mcg/dL
- 1-5 years: 5.9-15.0 mcg/dL
- 6-10 years: 6.0-13.9 mcg/dL
- 11-19 years: 5.9-13.2 mcg/dL
- > or =20 years: 4.8-12.7 mcg/dL

For SI unit Reference Values, see:

**Clinical References:**
about 75% of diagnoses are made after the death of the patient. In contrast, Acanthamoeba species and Balamuthia mandrillaris usually cause a subacute CNS illness, usually in immunocompromised adults, called granulomatous amebic encephalitis (GAE). The presentation of GAE can mimic a brain abscess, aseptic or chronic meningitis, or CNS malignancy. The amebae may enter the nasal sinuses like Naegleria fowleri or can disseminate to the CNS from the lungs or a primary skin lesion. These amebae are usually identified by microscopic examination of cerebrospinal fluid (CSF) or brain tissue and agar culture. Culture is more sensitive than microscopy alone, but takes up to 7 days to produce a positive result. Also, B mandrillaris will not grow in routine culture. Real-time PCR offers a rapid and sensitive alternative to microscopy and culture.

Useful For: Aids in the diagnosis of primary amebic meningoencephalitis and granulomatous amebic encephalitis in spinal fluid and tissue in conjunction with clinical findings

Interpretation: A positive result indicates the presence of free-living amoeba DNA and is consistent with active or recent infection. While positive results are highly specific indicators of disease, they should be correlated with symptoms and clinical findings of primary amebic meningoencephalitis and granulomatous amebic encephalitis.

Reference Values:
Negative


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**FFRED**

**Friedreich Ataxia Repeat Expansion Analysis - Unknown Mutation**

**Reference Values:**
A final report will be attached in MayoAccess.

**FFRBS**

**Friedreich Ataxia, Frataxin, Quantitative, Blood Spot**

**Clinical Information:** Friedreich ataxia (FA) is an autosomal recessive disease affecting approximately 1:50,000 Caucasians. The disease is clinically characterized by progressive spasticity, ataxia, dysarthria, absent lower limb reflexes, sensory loss, and scoliosis. Hypertrophic cardiomyopathy is present in approximately two-thirds of patients and is the most frequent cause of premature death in individuals with FA. Although most individuals begin experiencing initial symptoms between 10 and 15 years of age, atypical late-onset forms with initial symptoms presenting after age 25 do occur. FA is caused by mutations in the FXN gene encoding a mitochondrial protein, frataxin. Mutations in this gene lead to a reduced expression of frataxin, which causes the clinical manifestations of the disease. Approximately 98% of individuals with FA have a homozygous expansion of the GAA trinucleotide repeat in intron 1 of FXN. The remaining 2% of FA patients have the trinucleotide expansion on 1 allele and a point mutation or deletion on the second allele. Normal alleles contain between 5 to 33 GAA repeats. Disease-causing alleles typically range from 66 to 1,700 repeats, though the majority of individuals with FA have repeats ranging from 600 to 1,200. Historically, FA has been diagnosed by use of a DNA-based molecular test to detect the presence of the GAA expansion. Unfortunately, testing for the triplet repeat expansion will miss those patients with point mutations or deletions. Moreover, a molecular-based analysis is not able to effectively monitor treatment, is not amenable to multiplexing with other disease analytes, nor can it be efficiently utilized for population screening. In contrast, a protein-based assay measuring concentration of frataxin is suitable for both diagnosis as well as treatment monitoring in individuals with FA.

**Useful For:** Diagnosing individuals with Friedreich ataxia in blood spot specimens Monitoring frataxin levels in patients with Friedreich ataxia
Interpretation: Normal results (> or =15 ng/mL for pediatric and > or =21 ng/mL for adult patients) in properly submitted specimens are not consistent with Friedreich ataxia. For results outside the normal reference range an interpretative comment will be provided.

Reference Values:
Pediatric (<18 years) normal frataxin: > or =15 ng/mL
Adults (> or =18 years) normal frataxin: > or =21 ng/mL


Friedreich Ataxia, Frataxin, Quantitative, Whole Blood

Clinical Information: Friedreich ataxia (FA) is an autosomal recessive disease affecting approximately 1:50,000 Caucasians. The disease is clinically characterized by progressive spasticity, ataxia, dysarthria, absent lower limb reflexes, sensory loss, and scoliosis. Hypertrophic cardiomyopathy is present in approximately two-thirds of patients and is the most frequent cause of premature death in individuals with FA. Although most individuals begin experiencing initial symptoms between 10 and 15 years of age, atypical late-onset forms with initial symptoms presenting after age 25 do occur. FA is caused by mutations in the FXN gene encoding a mitochondrial protein, frataxin. Mutations in this gene lead to a reduced expression of frataxin, which causes the clinical manifestations of the disease. Approximately 98% of individuals with FA have a homozygous expansion of the GAA trinucleotide repeat in intron 1 of FXN. The remaining 2% of FA patients have the trinucleotide expansion on 1 allele and a point mutation or deletion on the second allele. Normal alleles contain between 5 to 33 GAA repeats. Disease-causing alleles typically range from 66 to 1,700 repeats, though the majority of individuals with FA have repeats ranging from 600 to 1,200. Historically, FA has been diagnosed by use of a DNA-based molecular test to detect the presence of the GAA expansion. Unfortunately, testing for the triplet repeat expansion will miss those patients with point mutations or deletions. Moreover, a molecular-based analysis is not able to effectively monitor treatment, is not amenable to multiplexing with other disease analytes, nor can it be efficiently utilized for population screening. In contrast, a protein-based assay measuring concentration of frataxin is suitable for both diagnosis as well as treatment monitoring in individuals with FA.

Useful For: Diagnosing individuals with Friedreich ataxia in whole blood specimens Monitoring frataxin levels in patients with Friedreich ataxia

Interpretation: Normal results (> or =19 ng/mL for pediatric and > or =21 ng/mL for adult patients) in properly submitted specimens are not consistent with Friedreich ataxia. For results outside the normal reference range an interpretative comment will be provided.

Reference Values:
Pediatric (<18 years) normal frataxin: > or =19 ng/mL
Adults (> or =18 years) normal frataxin: > or =21 ng/mL


Frozen section, 1st block (Bill Only)
**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**PCAFS**

113334

**Frozen section, addl blocks (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**FRUCT**

81610

**Fructosamine, Serum**

**Clinical Information:** Fructosamine is a general term, which applies to any glycated protein. It is formed by the nonenzymatic reaction of glucose with the a- and e-amino groups of proteins to form intermediate compounds called aldimines. These aldimines may dissociate or undergo an Amadori rearrangement to form stable ketoamines called fructosamines. This nonenzymatic glycation of specific proteins in vivo is proportional to the prevailing glucose concentration during the lifetime of the protein. Therefore, glyated protein measurement in the diabetic patient is felt to be a better monitor of long-term glycemic control than individual or sporadic glucose determinations. The best known of these proteins is glyated hemoglobin which is often measured as hemoglobin A1c, and reflects glycemic control over the past 6 to 8 weeks. In recognition of the need for a measurement that reflects intermediate-term glycemic control and was easily automated, a nonspecific test, termed fructosamine, was developed. Since albumin is the most abundant serum protein, it accounts for 80% of the glycated serum proteins, and thus, a high proportion of the fructosamine. Although a large portion of the color generated in the reaction is contributed by glycated albumin, the method will measure all proteins, each with a different half-life and different levels of glycation.

**Useful For:** Assessing intermediate-term glycemic control

**Interpretation:** In general, fructosamine reflects glycemic control in diabetic patients over the previous 2 to 3 weeks. High values indicate poor control.

**Reference Values:**
200-285 mcmol/L

**Clinical References:**

**FROS2**

92187

**Fructose, Qualitative, Semen**

**Clinical Information:** Fructose is produced in the male reproductive tract by the seminal vesicles and is released into the semen during ejaculation. Fructose is the energy source for sperm motility.

**Useful For:** Fructose testing should be considered for patients with azoosperma and low volume ejaculates to establish the origin of the azoosperma

**Interpretation:** A positive (indicated by color change) fructose is considered normal. A semen specimen that contains no sperm (azoosperma) and is fructose negative may indicate an absence of the seminal vesicles, absence of the vas deferens in the area of the seminal vesicles, or an obstruction at the level of the seminal vesicles.

**Reference Values:**
Positive

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**FFPG**

**Fruit Panel IgG**

**Reference Values:**

<table>
<thead>
<tr>
<th>Fruit</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple IgG</td>
<td>&lt; 2.0 mcg/mL</td>
</tr>
<tr>
<td>Apricot IgG</td>
<td>&lt; 2.0 mcg/mL</td>
</tr>
<tr>
<td>Banana IgG</td>
<td>&lt; 2.0 mcg/mL</td>
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<td>Blueberry IgG</td>
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<td>Grape IgG</td>
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<tr>
<td>Orange IgG</td>
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<td>Papaya IgG</td>
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<td>Pear IgG</td>
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<tr>
<td>Pineapple IgG</td>
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<tr>
<td>Plum IgG</td>
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</tr>
<tr>
<td>Raspberry IgG</td>
<td>&lt; 2.0 mcg/mL</td>
</tr>
<tr>
<td>Strawberry IgG</td>
<td>&lt; 2.0 mcg/mL</td>
</tr>
</tbody>
</table>

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**GFDZ**

**FTCD Gene, Full Gene Analysis**

**Clinical Information:** Glutamate formiminotransferase deficiency is an autosomal recessive inborn error of folate and histidine metabolism caused by a deficiency of the enzyme, glutamate formiminotransferase-cyclodeaminase, which is encoded at the FTCD loci on chromosome 21q22.3. Glutamate formiminotransferase deficiency presents as a clinical spectrum that ranges from asymptomatic to severe. Individuals with the severe form of disease are reported to have mental and physical retardation and anemia, whereas the mild form is associated with a lesser degree of developmental delay. Of note, the association of the enzyme deficiency with mental retardation has been disputed in the literature. An elevated amount of urine formiminoglutamate (FIGLU) is a cardinal sign of glutamate formiminotransferase deficiency for both the severe and mild clinical phenotypes. However, higher levels of urine FIGLU are observed in patients with milder forms of the disease and these levels occur in the absence of histidine loading; whereas the presence of FIGLU in the urine is typically only observed in severe cases after L-histidine administration. In addition, the severe form of disease is associated with elevated serum folate levels, whereas the milder form of disease is not. As there are discrepancies in FIGLU and serum folate levels among affected individuals, confirmation of suspected cases of glutamate formiminotransferase deficiency may require a liver biopsy for enzymology or the identification of 2 disease-causing mutations in the FTCD gene. Identification of 2 FTCD mutations establishes a molecular diagnosis of glutamate formiminotransferase deficiency, and rules out other diseases associated with high levels of urine FIGLU, such as folate or methylcobalamin deficiencies. Evaluation of the FTCD gene by molecular genetic testing is recommended as a second-tier test subsequent to a positive newborn screen or biochemical test.

**Useful For:** Second-tier test for confirming glutamate formiminotransferase deficiency (indicated by biochemical testing or newborn screening) Ruling out other diseases associated with high levels of urine formiminoglutamate Carrier screening in cases where there is a family history of glutamate formiminotransferase deficiency but disease-causing mutations have not been identified in an affected individual.
**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Fungal Culture, Blood**

**Clinical Information:** Due to the high mortality rate from fungemia, the expeditious detection and identification of fungi from the patient's blood can have great diagnostic prognostic importance. Risk factors for fungemia include, but are not limited to, extremes of age, immunosuppression, and those individuals with burns or indwelling intravascular devices.

**Useful For:** Diagnosis and treatment of the etiologic agents of fungemia Select patient population that presents with signs and symptoms of sepsis, especially fever of unknown origin

**Interpretation:** Positive cultures of yeast and filamentous fungi are reported with the organism identification. Positive cultures are usually an indication of infection and are reported as soon as detected. Correlation of culture results and the clinical situation is required for optimal patient management. A final negative report is issued after 30 days of incubation.

**Reference Values:**
Negative
If positive, notification is made as soon as the positive culture is detected or identified.

**Clinical References:**

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**Fungal Culture, Dermal**

**Clinical Information:** Fungal infections of keratinized tissues (hair, skin, nails) can be caused by dermatophytic fungi belonging to the genera Epidermophyton, Microsporum, and Trichophyton. Opportunistic superficial infections resembling dermatophytoses may be caused by yeasts or by unrelated filamentous fungi that are normally saprobes or plant pathogens. Dermatophytes are usually unable to penetrate deeper tissues. Infection may range from mild to severe.

**Useful For:** Recovery and identification of dermatophyte fungi from hair, skin, and nail infection specimens

**Interpretation:** Positive cultures are reported with organism identification. Negative reports are issued after 30 days incubation.

**Reference Values:**
Negative
If positive, fungus or yeast will be identified.

**Clinical References:** Borman AM, Summerbell RC: Trichophyton, Microsporum,

**FGEN 84389**

**Fungal Culture, Routine**

**Clinical Information:** Many fungi in the environment cause disease in immunocompromised human hosts. Accordingly, the range of potential pathogenic fungi has increased as the number of immunosuppressed individuals (e.g., persons with AIDS, patients receiving chemotherapy or transplant rejection therapy) has increased. Isolation and identification of the infecting fungus in the clinical laboratory can help guide patient care.

**Useful For:** Diagnosing fungal infections from specimens other than blood, skin, hair, nails, and vagina (separate tests are available for these specimen sites)

**Interpretation:** Positive cultures of yeast and filamentous fungi are reported with the organism identification. The clinician must determine whether or not the presence of an organism is significant. A final negative report is issued after 24 days of incubation.

**Reference Values:**

Negative

If positive, fungus will be identified.


**FVAG 5184**

**Fungal Culture, Vaginal**

**Clinical Information:** Candidal vulvovaginitis is believed to be the most frequent or second most frequent vaginal infection. Depending on the geographical area, its prevalence in women is estimated to be in the range of 5% to 20%. Besides *Candida albicans*, *C glabrata*, and *C tropicalis* are the most frequently isolated *Candida* species both from vulvo-vaginitis patients and from healthy carriers.

**Useful For:** Monitoring therapy for vulvovaginitis Managing chronic recurring disease Determining the etiology of infectious vaginitis when other tests have been uninformative

**Interpretation:** Meaningful diagnosis of vaginal candidiasis requires that 1) yeast are demonstrable in the affected area and 2) clinical symptoms and signs are consistent with the disease. Since in up to 20% of healthy women, yeast cells are part of the normal vaginal flora, the presence of Candida on culture may be meaningless or misleading unless other clinical factors are considered.

**Reference Values:**

Negative

If positive, yeast will be identified.

**Clinical References:**


**FS 84390**

**Fungal Smear**

**Clinical Information:** Many fungi in the environment cause disease in severely compromised human hosts. Accordingly, the range of potential pathogenic fungi has increased as the number of
Immunosuppressed individuals (persons with AIDS, patients receiving chemotherapy or transplant rejection therapy, etc) has increased. Few fungal diseases can be diagnosed clinically; most are diagnosed by isolating and identifying the infecting fungus in the clinical laboratory.

**Useful For:** Detection of fungi in clinical specimens

**Interpretation:** Positive slides are reported as one or more of the following: yeast or hyphae present, organism resembling Blastomyces dermatitidis, Histoplasma capsulatum, Coccidioides immitis, Cryptococcus neoformans, or Malassezia furfur.

**Reference Values:**
Negative


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**Fungitell, BAL**

**Clinical Information:** The Fungitell Beta D Glucan assay detects (1,3) Beta-D-glucan from the following pathogens: Candida spp., Acremonium, Aspergillus spp., Coccidioides immitis, Fusarium spp., Histoplasma capsulatum, Trichosporon spp., Sporothrix schenckii, Saccharomyces cerevisiae, and Pneumocystis jiroveci. The Fungitell Beta-D Glucan assay does not detect certain fungal species such as the genus Cryptococcus, which produces very low levels of (1,3) Beta-D-glucan, nor the Zygomycetes, such as Absidia, Mucor, and Rhizopus, which are not known to produce (1,3) Beta-D-glucan. Studies indicate Blastomyces dermatitidis is usually not detected due to little (1,3) Beta-D-glucan produced in the yeast phase.

**Interpretation:** The performance characteristics of the Fungitell assay in BAL have been determined by Viracor-Eurofins; there are no established criteria for the interpretation of Fungitell results from BAL fluid. Research studies have evaluated the use of the Fungitell assay in BAL in both immunocompromised patients (Mycopathologia (2013) 175:33-41) and acute eosinophilic pneumonia (Chest (2003) 123:1302-1307).

**Reference Values:**
A reference range for specimens other than serum has not been established.

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**Fungitell, bronch wash**

**Clinical Information:** The Fungitell Beta D Glucan assay detects (1,3) Beta-D-glucan from the following pathogens: Candida spp., Acremonium, Aspergillus spp., Coccidioides immitis, Fusarium spp., Histoplasma capsulatum, Trichosporon spp., Sporothrix schenckii, Saccharomyces cerevisiae, and Pneumocystis jiroveci. The Fungitell Beta-D Glucan assay does not detect certain fungal species such as the genus Cryptococcus, which produces very low levels of (1,3) Beta-D-glucan, nor the Zygomycetes, such as Absidia, Mucor, and Rhizopus, which are not known to produce (1,3) Beta-D-glucan. Studies indicate Blastomyces dermatitidis is usually not detected due to little (1,3) Beta-D-glucan produced in the yeast phase.

**Interpretation:** The performance characteristics of the Fungitell assay in bronchial wash have been determined by Viracor-IBT Laboratories; there are no established criteria for the interpretation of Fungitell results from bronchial wash fluid. Research studies have evaluated the use of the Fungitell assay in BAL in both immunocompromised patients (Mycopathologia (2013) 175:33-41) and acute eosinophilic pneumonia (Chest (2013) 123:1302-1307).

**Reference Values:**
A reference range for specimens other than serum has not been established.
**Fungitell, CSF**

**Clinical Information:** The Fungitell Beta-D Glucan assay is indicated for the presumptive diagnosis of invasive fungal disease through detection of elevated levels of (1,3)-Beta-D-glucan in serum. Normal human serum contains low levels of (1,3)-Beta-D-glucan, typically 10 to 40 pg/mL, presumably from commensal yeasts present in the alimentary canal and gastrointestinal tract. However, (1,3)-Beta-D-glucan is sloughed from the cell walls during the life cycle of most pathogenic fungi. Thus, monitoring serum for evidence of elevated and rising levels of (1,3)-Beta-D-glucan provides a convenient surrogate marker for invasive fungal disease. The Fungitell Beta-D Glucan assay detects (1,3)-Beta-D-glucan from the following pathogens: Candida spp., Acremonium, Aspergillus spp., Coccidioides immitis, Fusarium spp., Histoplasma capsulatum, Trichosporon spp., Sporothrix schenckii, Saccharomyces cerevisiae, and Pneumocystis jiroveci. The Fungitell Beta-D Glucan assay does not detect certain fungal species such as the genus Cryptococcus, which produces very low levels of (1,3)-Beta-D-glucan, nor the Zygomycetes, such as Absidia, Mucor, and Rhizopus, which are not known to produce (1,3)-Beta-D-glucan. Studies indicate Blastomyces dermatitidis is usually not detected due to little (1,3)-Beta-D-glucan produced in the yeast phase.

**Interpretation:** The performance characteristics of the Fungitell assay in CSF have been determined by Viracor-IBT Laboratories; there are no established criteria for the interpretation of Fungitell results from CSF fluid. Research studies have evaluated the use of the Fungitell assay in CSF during a fungal meningitis outbreak (J. Clin. Microbiol. 2013, 51(4):1285-1287).

**Reference Values:**
A reference range for specimens other than serum has not been established.

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**Fungitell, Serum**

**Interpretation:** The Fungitell assay does not detect certain fungal species such as the genus Cryptococcus (Tanaka et. al. 1991) which produces very low levels of (1-3)-Beta-D-Glucan. The assay also does not detect the Zygomycetes such as Absidia, Mucor and Rhizopus (Mitsuya et al. 1994) which are not known to produce (1-3)-Beta-D-Glucan. In addition, the yeast phase of Blastomyces dermatitidis produces little (1-3)-Beta-D-Glucan and may not be detected by the assay (Girouard et al. 2007).

**Reference Values:**
Less than 60 pg/mL. Glucan values of less than 60 pg/mL are interpreted as negative. Glucan values of 60 to 79 pg/mL are interpreted as indeterminate, and suggest a possible fungal infection. Additional sampling and testing of sera is required to interpret the results.

Glucan values of greater than or equal to 80 pg/mL are interpreted as positive. Due to the potential for environmental contamination when transferred to pour-off tubes, which can lead to false positive results, interpret positive results from samples provided in pour-off tubes with caution. Results should be used in conjunction with clinical findings, and should not form the sole basis for a diagnosis or treatment decision. The Fungitell test is approved or cleared for in vitro diagnostic use by the U.S. Food and Drug Administration. Modifications to the approved package insert have been made and the performance characteristics for these modifications were determined by Viracor Eurofins.

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**Furosemide (Lasix)**

**Reference Values:**
Expected serum furosemide concentration in patients on usual daily dosages: Up to 5.0 ug/mL

Toxic: greater than 50.0 ug/mL

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**FUS Immunostain, Technical Component Only**

**Clinical Information:** FUS (also known as "translated in liposarcoma" TLS) protein is a
multifunctional DNA- and RNA-binding protein. Studies have shown the cause of familial amyotrophic lateral sclerosis (ALS) to be a mutation in the gene encoding the FUS protein. FUS has been linked to other neurodegenerative diseases including frontotemporal lobar dementia (FTLD), and neuronal intermediate filament inclusion disease (NIFID).

**Useful For:** Identification of frontotemporal lobar dementia (FTLD)

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Fusarium moniliforme, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
Reference Values:
Class IgE (kU/L) Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


**Fusarium oxysporum/vasinfectum IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.4 Positive 4 17.5-49.9 Strong Positive 5 50.00-99.9 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:
<0.35 kU/L

**Gaba, Serum**

**Clinical Information:** Gabapentin is an antiepileptic drug that is effective in treating seizures, neuropathies, and a variety of neurological and psychological maladies. Although designed as a gamma-aminobutyric acid (GABA) analogue, gabapentin does not bind to GABA receptors, nor does it affect the neuronal uptake or degradation of GABA. In fact, the precise mechanism by which it exerts its analgesic and anticonvulsant effects is unknown. After oral administration and absorption, gabapentin circulates essentially unbound to serum proteins. In addition, gabapentin does not undergo hepatic metabolism unlike most other antiepileptic drugs and is eliminated almost entirely by renal excretion with a clearance that approximates the glomerular filtration rate. The elimination half-life is 5 to 7 hours in patients with normal renal function. Since gabapentin does not bind to serum proteins, it does not exhibit pharmacokinetic variability and interactions with other highly protein-bound medications (ie, phenytoin). In addition, the lack of hepatic metabolism eliminates the interactions with other hepatically cleared medications which can induce/inhibit hepatic drug metabolizing enzyme systems (cytochrome P450s). Therefore, gabapentin serum concentrations are not changed following the addition or discontinuation of other common anticonvulsants (ie, phenobarbital, phenytoin, carbamazepine, or valproic acid), nor are their serum concentration altered upon the addition or discontinuation of gabapentin. In general, adverse effects with gabapentin are infrequent and usually resolve with continued treatment. The most common side effects include somnolence, dizziness, ataxia, and fatigue. Experience to date indicated that gabapentin is safe and relatively nontoxic.

**Useful For:** Monitoring serum gabapentin concentrations Assessing compliance Adjusting dosage in patients

**Interpretation:** Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next dose). Most individuals display optimal response to gabapentin with serum levels of 2 to 20 mcg/mL. Some individuals may respond well outside of this range, or may display toxicity within the
therapeutic range; thus, interpretation should include clinical evaluation. Some patients require high doses to achieve response, resulting in concentrations as high as 80 mcg/mL. Dosage reduction should be based on signs of toxicity, not the serum concentration.

**Reference Values:**

2.0-20.0 mcg/mL

Toxic Range: > or =25.0 mcg/mL

**Clinical References:**

**FGABA**

GABAPENTIN, URINE

**Reference Values:**

Reference Range: Not Established

Units: ug/mL

**GDU**

GADOLINIUM, 24 HOUR, URINE

**Clinical Information:** Gadolinium is a member of the lanthanide series of the periodic table of elements and is considered a nonessential element. Due to its paramagnetic properties, chelated gadolinium is commonly employed as contrast media (gadolinium-based contrast agents: GBCA) for magnetic resonance imaging and computer tomography scanning. Gadolinium is primarily eliminated via the kidneys, so exposure can be prolonged in patients with renal insufficiency. In healthy subjects with normal renal function, the plasma half-life of gadolinium is approximately 90 minutes (1.5 hours). Patients with reduced renal function and some patients with normal renal function may exhibit a prolonged gadolinium elimination half-life. To date, the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF). NSF is a relatively uncommon condition in which fibrous plaques develop in the dermis and, often, in deeper connective tissues. Reported cases have occurred almost exclusively in patients with severe renal disease, and almost all have been associated with prior use of GBCAs. NSF is a painful skin disease characterized by thickening of the skin, which can involve the joints and cause significant limitation of motion within weeks to months. Over the past decade, changes in clinical practice guidelines have almost completely eliminated the incidence of NSF. However, the association of NSF and observed elevated gadolinium concentrations is still not fully understood.

**Useful For:** Assessing chronic exposure and monitoring effectiveness of dialysis in a 24-hour urine collection

**Interpretation:** Elevated urine gadolinium results collected more than 96 hours after administration of a gadolinium-based contrast agent only confirms past exposure, or continued exposure through anthropogenic sources, and prolonged elimination of gadolinium. Gadolinium also has been shown to be present in some municipal water sources which may contribute to the observation of low concentrations of gadolinium in patients who never have been exposed to gadolinium-based contrast agents (GBCA). Elevated gadolinium in a specimen collected more than 96 hours after contrast media infusion does not indicate risk of nephrogenic systemic fibrosis (NSF).

**Reference Values:**

0-17 years: not established
> or =18 years: <0.7 mcg/24 hour

Gadolinium, Dermal, Tissue

Clinical Information: Gadolinium is a member of the lanthanide series of the periodic table of elements and is considered a nonessential element. Due to its paramagnetic properties, chelated gadolinium is commonly employed as contrast media (gadolinium-based contrast agents: GBCA) for magnetic resonance imaging and computer tomography scanning. Gadolinium is primarily eliminated via the kidneys, so exposure can be prolonged in patients with renal insufficiency. In healthy subjects with normal renal function, the plasma half-life of gadolinium is approximately 90 minutes (1.5 hours). Patients with reduced renal function and some patients with normal renal function may exhibit a prolonged gadolinium elimination half-life. To date, the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF). NSF is a relatively uncommon condition in which fibrous plaques develop in the dermis and, often, in deeper connective tissues. Reported cases have occurred almost exclusively in patients with severe renal disease, and almost all have been associated with prior use of GBCAs. NSF is a painful skin disease characterized by thickening of the skin, which can involve the joints and cause significant limitation of motion within weeks to months. Over the past decade, changes in clinical practice guidelines have almost completely eliminated the incidence of NSF. However, the association of NSF and observed elevated gadolinium concentrations is still not fully understood.

Useful For: Evaluation of dermal tissue for gadolinium

Interpretation: Elevated gadolinium (>0.5 mcg/g) observed in dermal tissue specimens collected more than 96 hours after administration of gadolinium-based contrast agents indicates some gadolinium deposition. In a small internal study (n=13), patients with histologically confirmed nephrogenic systemic fibrosis (NSF) and a history of renal failure and exposure to gadolinium-based contrast agents (GBCA) had gadolinium concentrations in the range of 6.3 to 348.7 mcg/g in affected tissues. However, unaffected tissues from gadolinium-exposed subjects showed gadolinium concentrations in the range of 0.6 to 68.2 mcg/g. A detectable gadolinium concentration in tissue suggests recent or past exposure to GBCA.

Reference Values:
<0.5 mcg/g

Gadolinium, Serum

**Clinical Information:** Gadolinium is a member of the lanthanide series of the periodic table of elements and is considered a nonessential element. Due to its paramagnetic properties, chelated gadolinium is commonly employed as contrast media (gadolinium-based contrast agents: GBCA) for magnetic resonance imaging and computer tomography scanning. Gadolinium is primarily eliminated via the kidneys, so exposure can be prolonged in patients with renal insufficiency. In healthy subjects with normal renal function, the plasma half-life of gadolinium is approximately 90 minutes (1.5 hours). Patients with reduced renal function and some patients with normal renal function may exhibit a prolonged gadolinium elimination half-life. To date, the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF). NSF is a relatively uncommon condition in which fibrous plaques develop in the dermis and, often, in deeper connective tissues. Reported cases have occurred almost exclusively in patients with severe renal disease, and almost all have been associated with prior use of GBCAs. NSF is a painful skin disease characterized by thickening of the skin, which can involve the joints and cause significant limitation of motion within weeks to months. Over the past decade, changes in clinical practice guidelines have almost completely eliminated the incidence of NSF. However, the association of NSF and observed elevated gadolinium concentrations is still not fully understood.

**Useful For:** An aid in documenting past exposure to gadolinium-based contrast agents in serum specimens

**Interpretation:** Elevated gadolinium observed in serum specimens drawn more than 96 hours after administration of gadolinium-containing contrast media is not typical of most patients with normal renal function, and may indicate prolonged elimination of gadolinium and exposure to anthropogenic sources.

**Reference Values:** <0.5 ng/mL

**Clinical References:**

Gadolinium/Creatinine Ratio, Random, Urine

**Clinical Information:** Gadolinium is a member of the lanthanide series of the periodic table of elements and is considered a nonessential element. Due to its paramagnetic properties, chelated gadolinium is commonly employed as contrast media (gadolinium-based contrast agents: GBCA) for magnetic resonance imaging and computer tomography scanning. Gadolinium is primarily eliminated via the kidneys, so exposure can be prolonged in patients with renal insufficiency. In healthy subjects with normal renal function, the plasma half-life of gadolinium is approximately 90 minutes (1.5 hours). Patients with reduced renal function and some patients with normal renal function may exhibit a prolonged gadolinium elimination half-life. To date, the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF). NSF is a relatively uncommon condition in which fibrous plaques develop in the dermis and, often, in deeper connective tissues. Reported cases have occurred almost exclusively in patients with severe renal disease, and almost all have been associated with prior use of GBCAs. NSF is a painful skin disease characterized by thickening of the skin, which can involve the joints and cause significant limitation of motion within weeks to months. Over the past decade, changes in clinical practice guidelines have almost completely eliminated the incidence of NSF. However, the association of NSF and observed elevated gadolinium concentrations is still not fully understood.

**Useful For:** An aid in documenting past exposure to gadolinium-based contrast agents in serum specimens

**Interpretation:** Elevated gadolinium observed in serum specimens drawn more than 96 hours after administration of gadolinium-containing contrast media is not typical of most patients with normal renal function, and may indicate prolonged elimination of gadolinium and exposure to anthropogenic sources.

**Reference Values:** <0.5 ng/mL

**Clinical References:**
gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF). NSF is a relatively uncommon condition in which fibrous plaques develop in the dermis and, often, in deeper connective tissues. Reported cases have occurred almost exclusively in patients with severe renal disease, and almost all have been associated with prior use of GBCA. NSF is a painful skin disease characterized by thickening of the skin, which can involve the joints and cause significant limitation of motion within weeks to months. Over the past decade, changes in clinical practice guidelines have almost completely eliminated the incidence of NSF. However, the association of NSF and observed elevated gadolinium concentrations is still not fully understood.

**Useful For:** Assessing chronic exposure and monitoring effectiveness of dialysis in a random urine collection

**Interpretation:** Elevated urine gadolinium results collected more than 96 hours after administration of a gadolinium-based contrast agent only confirms past exposure, or continued exposure through anthropogenic sources, and prolonged elimination of gadolinium. Gadolinium also has been shown to be present in some municipal water sources, which may contribute to the observation of low concentrations of gadolinium in patients who never have been exposed to gadolinium-based contrast agents (GBCA). Elevated gadolinium in a specimen collected more than 96 hours after contrast media infusion does not indicate risk of nephrogenic systemic fibrosis (NSF).

**Reference Values:**
0-17 years: not established
> or =18 years: <0.8 mcg/g creatinine

**Clinical References:**

**GATOL Galactitol, Quantitative, Urine**

**Clinical Information:** Galactosemia is an autosomal recessive disorder that results from a deficiency of 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridylyltransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near complete deficiency of the GALT enzyme is life threatening. If left untreated, complications include liver failure, sepsis, cognitive and intellectual disabilities, and death. Galactosemia is treated with a galactose-free diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, children with galactosemia remain at increased risk for developmental delays, speech problems, abnormalities of motor function, and females are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000. Galactose levels may be continuously elevated in individuals affected with galactosemia even with a galactose-restricted diet regimen due to an endogenous production of galactose. The reduction of galactose to galactitol is an alternate pathway of galactose disposition when galactose metabolism is impaired. The excretion of abnormal quantities of galactitol in the urine of patients is characteristic of this disorder, and patients may have abnormal levels of galactitol even with dietary compliance. Daily consumption of galactose may cause urine levels to rise thus providing information on effectiveness of or
compliance with treatment, but unlike erythrocyte galactose-1-phosphate (GAL1P) and plasma galactose, urine galactitol levels usually do not provide insight into acute and transient effects of galactose intake.

**Useful For:** Monitoring effectiveness of treatment in patients with galactosemia Establishing a baseline level prior to initiating treatment for galactosemia

**Interpretation:** The concentration of galactitol is provided along with reference ranges for patients with galactosemia and normal controls.

**Reference Values:**
0-11 months: <109 mmol/mol creatinine
1-3 years: <52 mmol/mol creatinine
4â€“17 years: <16 mmol/mol creatinine
> or =18 years: <13 mmol/mol creatinine


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**Galactocerebrosidase, Leukocytes**

**Clinical Information:** Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by a deficiency of galactocerebrosidase. A deficiency of this enzyme leads to an accumulation of galactosylceramide causing severe demyelination throughout the brain. Krabbe disease is primarily caused by mutations in the GAGL gene, and it has an estimated frequency of 1 in 100,000 births. Although rare, a few infants with an early onset Krabbe disease phenotype due to deficiency of saposin A (SAP-A) have been found. Saposin-A is a sphingolipid activator protein that assists galactocerebrosidase in its action on galactosylceramide. Severely affected individuals typically present between 3 to 6 months of age with increasing irritability and sensitivity to stimuli. Rapid neurodegeneration including white matter disease follows with death usually occurring by age 2. Some individuals have later onset forms of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression presenting anywhere from age 6 months to the seventh decade of life. The clinical course of Krabbe disease can be variable, even within the same family. Newborn screening for Krabbe disease has been implemented in some states. The early (presymptomatic) identification and subsequent testing of infants at risk for Krabbe disease may be helpful in reducing the morbidity and mortality associated with this disease. While treatment is mostly supportive, hematopoietic stem cell transplantation has shown some success if performed prior to onset of neurologic damage. Reduced or absent galactocerebrosidase in leukocytes can indicate a diagnosis of Krabbe disease, however a number of polymorphisms in the GAGL gene have been identified that result in reduced galactocerebrosidase activity in vitro, but do not cause disease. Molecular sequencing of the GAGL gene (KRABZ / Krabbe Disease, Full Gene Analysis and Large [30 kb] Deletion, PCR) is necessary for differentiating polymorphisms from disease-causing mutations in affected patients and for carrier detection in family members.

**Useful For:** Diagnosis of Krabbe disease

**Interpretation:** Values below the reference range are consistent with a diagnosis of Krabbe disease.

**Reference Values:**
> or =1.20 nmol/h/mg protein

**GALK**

**Clinical Information:** Galactokinase (GALK) deficiency is the second most common form of galactosemia, affecting approximately 1 in 250,000 live births, with a higher frequency in the Romani population. Individuals with GALK deficiency have a milder clinical presentation than that seen in patients with classic galactosemia, galactose-1-phosphate uridyltransferase (GALT) deficiency. The major clinical manifestation is bilateral juvenile cataracts. GALK deficiency is treated with a lactose-restricted diet. Early treatment may prevent or reverse the formation of cataracts. In GALK deficiency, erythrocyte galactose-1-phosphate levels are generally normal and plasma galactose levels are generally elevated. The diagnosis is established by demonstrating deficient GALK enzyme activity in erythrocytes. Testing for GALK deficiency should be performed when there is a suspicion of galactosemia, either based upon the patient's clinical presentation or laboratory studies and GALT deficiency has been excluded. Specimens sent for GALT analysis may be used for GALK testing if the original specimen was received in the laboratory within the stability parameters listed in Specimen Stability Information. GALK deficiency is caused by mutations in the GALK1 gene. Gene analysis is available from some commercial laboratories. Call 800-533-1710 for recommendations or contact information for laboratories that offer this testing. See Galactosemia Testing Algorithm in Special Instructions.

**Useful For:** Diagnosis of galactokinase deficiency, the second most common cause of galactosemia

**Interpretation:** An interpretive report will be provided. See Galactosemia Testing Algorithm in Special Instructions for additional information.

**Reference Values:**

> or =0.7 nmol/h/mg of hemoglobin

**Clinical References:**


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**GALP**

**Clinical Information:** Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridylyltransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life-threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death; even with survival, long-term intellectual disability can result. Galactosemia is treated by a lactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at...
increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births. A comparison of plasma and urine galactose and blood galactose-1-phosphate (Gal-1-P) levels may be useful in distinguishing among the 3 forms of galactosemia. See Galactosemia Testing Algorithm in Special Instructions for additional information. Deficiency Galactose (Plasma/Urine) Gal-1-P (Blood) GALK Elevated Normal GALT Elevated Elevated GALE Normal-Elevated Elevated

**Useful For:** Screening for galactosemia

**Interpretation:** Additional testing is required to investigate the cause of abnormal results. In patients with galactosemia, elevated galactose in plasma or urine may suggest ineffective dietary restriction or compliance; however, the concentration of galactose-1-phosphate in erythrocytes (GAL1P / Galactose-1-Phosphate [Gal-1-P], Erythrocytes) is the most sensitive index of dietary control. Increased concentrations of galactose may also be suggestive of severe hepatitis, biliary atresia of the newborn, and, in rare cases, galactose intolerance. If results are outside the normal range and galactosemia is suspected, additional testing to identify the specific enzymatic defect is required. Results should be correlated with clinical presentation and confirmed by specific enzyme or molecular analysis. See Galactosemia Testing Algorithm in Special Instructions for follow-up of abnormal newborn screening results, comprehensive diagnostic testing, and carrier testing. See GALT / Galactose-1-Phosphate Uridyltransferase (GALT), Blood for GALT testing, GALK / Galactokinase, Blood for GALK testing, and GALE / UDP-Galactose-4â€™ Epimerase (GALE), Blood for GALE testing.

**Reference Values:**
- 1-7 days: <5.4 mg/dL
- 8-14 days: <3.6 mg/dL
- >14 days: <2.0 mg/dL

**Clinical References:**

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**Galactose, Quantitative, Urine**

**Clinical Information:** Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridylyltransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life-threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death; even with survival, long-term intellectual disability can result. Galactosemia is treated by a galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births. A comparison of plasma and urine galactose and blood galactose-1-phosphate (Gal-1-P) levels may be useful in distinguishing among the 3 forms of galactosemia; however, these are only general patterns and further confirmatory testing would be required to make a diagnosis. Deficiency Galactose (Plasma/Urine) Gal-1-P (Blood) GALK Elevated Normal GALT Elevated Elevated GALE Normal-Elevated Elevated See Galactosemia Testing Algorithm in Special Instructions for additional information.
**Useful For:** Screening test for galactosemia in urine specimens

**Interpretation:** Additional testing is required to investigate the cause of abnormal results. In patients with galactosemia, elevated galactose in plasma or urine may suggest ineffective dietary restriction or compliance; however, the concentration of galactose-1-phosphate in erythrocytes (GAL1P / Galactose-1-Phosphate [Gal-1-P], Erythrocytes) is the most sensitive index of dietary control. Increased concentrations of galactose may also be suggestive of severe hepatitis, biliary atresia of the newborn and, in rare cases, galactose intolerance. If galactosemia is suspected, additional testing to identify the specific enzymatic defect is required. See Galactosemia Testing Algorithm in Special Instructions for follow-up of abnormal newborn screening results, comprehensive diagnostic testing, and carrier testing. Results should be correlated with clinical presentation and confirmed by specific enzyme or molecular analysis.

**Reference Values:**

<30 mg/dL

**Clinical References:**


**GAL1P**

**Galactose-1-Phosphate (Gal-1-P), Erythrocytes**

**Clinical Information:** Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridylytransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). Galactose-1-phosphate (Gal-1-P) accumulates in the erythrocytes of patients with galactosemia due to either GALT or GALE deficiency. The quantitative measurement of Gal-1-P (GAL1P / Galactose-1-Phosphate (Gal-1-P), Erythrocytes) is useful for monitoring compliance with dietary therapy for either deficiency. Gal-1-P is thought to be the causative factor for development of liver disease in these patients and, because of this, patients should maintain low levels and be monitored on a regular basis. The concentration of Gal-1-P in erythrocytes is the most sensitive index of dietary control. GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life-threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death; even with survival, long-term intellectual disability can result. Galactosemia due to GALT deficiency is treated by a galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births. Epimerase deficiency galactosemia can be categorized into 3 types: generalized, peripheral, and intermediate. Generalized epimerase deficiency galactosemia results in profoundly decreased enzyme activity in all tissues, whereas peripheral epimerase deficiency galactosemia results in decreased enzyme activity in red and white blood cells, but normal enzyme activity in all other tissues. This is compared with intermediate epimerase deficiency galactosemia, which results in decreased enzyme activity in red and white blood cells and less than 50% of normal enzyme levels in other tissues. Clinically, infants with generalized epimerase deficiency galactosemia develop symptoms such as liver and renal dysfunction and mild cataracts when on a normal milk diet, while infants with peripheral or intermediate epimerase deficiency galactosemia do not develop any symptoms. Generalized epimerase deficiency galactosemia is treated by a galactose- and lactose-restricted diet, which can improve or prevent the symptoms of renal and liver dysfunction and mild cataracts. Despite adequate treatment from an early age, individuals with generalized epimerase deficiency galactosemia remain at increased risk for developmental delay and intellectual disability. Unlike patients with classic galactosemia resulting from a GALT deficiency, females with generalized epimerase deficiency galactosemia experience normal puberty and are not at increased risk for premature
ovarian failure. Based upon reports by newborn screening programs, the frequency of epimerase deficiency galactosemia in the United States ranges from approximately 1 in 6,700 in African American infants to 1 in 70,000 in infants of European ancestry. See Galactosemia Testing Algorithm in Special Instructions.

**Useful For:** Monitoring dietary therapy of patients with galactosemia due to deficiency of galactose-1-phosphate uridylyltransferase or uridine diphosphate galactose-4-epimerase

**Interpretation:** The concentration of galactose-1-phosphate (Gal-1-P) is provided along with reference ranges for patients with galactosemia and normal controls. The recommended Gal-1-P goal for patients with galactosemia is less than 125 mcg/g of hemoglobin. See Galactosemia Testing Algorithm in Special Instructions for additional information.

**Reference Values:**
Non-galactosemic: 5-49 mcg/g of hemoglobin (<1 mg/dL)
Galactosemic on galactose restricted diet: 80-125 mcg/g of hemoglobin (1-4 mg/dL)
Galactosemic on unrestricted diet: >125 mcg/g of hemoglobin (>4 mg/dL)

**Clinical References:**

**Galactose-1-Phosphate Uridyltransferase (GALT), Blood**

**Clinical Information:** Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridylyltransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death; even with survival, long-term intellectual disability can occur. Galactosemia is treated by a galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births. Galactose-1-phosphate (Gal-1-P) accumulates in the erythrocytes of patients with galactosemia. The quantitative measurement of Gal-1-P is useful for monitoring compliance with dietary therapy. Gal-1-P is thought to be the causative factor for development of liver disease in these patients and, because of this, patients should maintain low levels and be monitored on a regular basis. Duarte-variant galactosemia (compound heterozygosity for the Duarte mutation, N314D, and a classic mutation) is generally associated with higher levels of enzyme activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Typically, individuals with Duarte-variant galactosemia have a milder phenotype, but are also often treated with a low galactose diet during infancy. The Los Angeles variant, which consists of N314D and a second mutation, L218L, is associated with higher levels of GALT enzyme activity than the Duarte-variant allele. Newborn screening for galactosemia is performed in all 50 US states, though the method by which potentially affected individuals are detected varies from state to state and may include the measurement of total galactose (galactose and Gal-1-P) and/or determining the activity of the GALT enzyme. The diagnosis of galactosemia is established by follow-up quantitative measurement of GALT enzyme activity. If enzyme levels are indicative of carrier or affected status, molecular testing for common GALT mutations may be performed. If 1 or both disease-causing mutations are not detected by targeted mutation analysis and biochemical testing has confirmed the diagnosis of galactosemia, sequencing of the GALT gene is available to identify private mutations. See Galactosemia Testing Algorithm in
Special Instructions for additional information.

**Useful For:** Diagnosis of galactose-1-phosphate uridylyltransferase deficiency, the most common cause of galactosemia. Confirmation of abnormal state newborn screening results.

**Interpretation:** An interpretive report will be provided. See Galactosemia Testing Algorithm in Special Instructions for additional information.

**Reference Values:**

> or =24.5 nmol/h/mg of hemoglobin

**Clinical References:**


**GALTP**

**Galactose-1-Phosphate Uridyltransferase Biochemical Phenotyping, Erythrocytes**

**Clinical Information:** Galactosemia is an autosomal recessive disorder that results from a deficiency of any 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridylyltransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). GALT deficiency is the most common cause of galactosemia and is often referred to as classic galactosemia. The complete or near-complete deficiency of GALT enzyme is life-threatening if left untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death; even with survival, long-term intellectual disability can result. Galactosemia is treated by a galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of classic galactosemia in the United States is approximately 1 in 30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births. Duarte-variant galactosemia (compound heterozygosity for the Duarte mutation, N314D, and a classic mutation) is generally associated with higher levels of enzyme activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Typically, individuals with Duarte-variant galactosemia have a milder phenotype, but are also often treated with a low galactose diet during infancy. The LA variant, which consists of N314D and a second mutation, L218L, is associated with higher levels of GALT enzyme activity than the Duarte-variant allele. In general, molecular genetic analysis with a panel of common mutations is typically performed to determine the specific genotype. If the enzymatic and molecular results are incongruent, biochemical phenotyping and/or molecular sequence analysis may be beneficial to help clarify results to determine a treatment strategy and recurrence risks. See Galactosemia Testing Algorithm in Special Instructions for additional information.

**Useful For:** Determining the biochemical phenotype for galactosemia when enzymatic and molecular results are incongruent.

**Interpretation:** An interpretive report will be provided. A quantitative galactose-1-phosphate uridylyltransferase level (GALT / Galactose-1-Phosphate Uridyltransferase [GALT], Blood) is required for accurate interpretation. See Galactosemia Testing Algorithm in Special Instructions for additional information.

**Reference Values:**

Descriptive report

**Clinical References:**


**FGA13 57566**

**Galactose-alpha-1,3-galactose (Alpha-Gal) IgE**

**Interpretation:**

**Reference Values:**

<0.35 kU/L

Previous reports (JACI 2009; 123:426-433) have demonstrated that patients with IgE antibodies to galactose-a-1,3-galactose are at risk for delayed anaphylaxis, angioedema, or urticaria following consumption of beef, pork, or lamb.

**GAL14 55071**

**Galactosemia Gene Analysis (14-Mutation Panel)**

**Clinical Information:** Classical galactosemia is an autosomal recessive disorder of galactose metabolism caused by mutations in the galactose-1-phosphate uridyltransferase (GALT) gene. The complete or near complete deficiency of the GALT enzyme is life threatening. If left untreated, complications include liver failure, sepsis, mental retardation, and death. Galactosemia is treated by a galactose-free diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, children with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. The prevalence of classic galactosemia is approximately 1 in 30,000. Duarte variant galactosemia (compound heterozygosity for the Duarte mutation, N314D and -119_-116delGTCA in cis [on the same chromosome], and a classic mutation in trans [on the opposite chromosome]) is generally associated with higher levels of enzyme activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Typically, individuals with Duarte variant galactosemia have a milder phenotype but are also often treated with a low-galactose diet during infancy. The Los Angeles (LA) variant, which consists of N314D without the presence of -119_-116delGTCA, is associated with normal levels of GALT enzyme activity. Newborn screening, which identifies potentially affected individuals by measuring total galactose (galactose and galactose-1-phosphate) and/or determining the activity of the GALT enzyme, varies from state to state. The diagnosis of galactosemia is established by follow-up quantitative measurement of GALT enzyme activity. If enzyme levels are indicative of carrier or affected status, molecular testing for common GALT mutations may be performed. If 1 or both disease-causing mutations are not detected by targeted mutation analysis and biochemical testing has confirmed the diagnosis of galactosemia, sequencing of the GALT gene is available to identify private mutations. The GALT gene maps to 9p13. Several disease-causing mutations are common in patients with classic galactosemia (G/G genotype). The most frequently observed is the Q188R classic mutation. This mutation accounts for 60% to 70% of classical galactosemia alleles. The S135L mutation is the most frequently observed mutation in African Americans and accounts for approximately 50% of the mutant alleles in this population. The K285N mutation is common in those of eastern European descent and accounts for 25% to 40% of the alleles in this population. The L195P mutation is observed in 5% to 7% of classical galactosemia. The 5 kb deletion is common in individuals of Ashkenazi Jewish descent. The Duarte mutation (N314D and -119_-116delGTCA) is observed in 5% of the general United States population. The rest of the mutations detected by this method (ie, D98N, S135L, T138M, M142K, F171S, Y209C, and Q344K) are all uncommon, but known to be recurrent in the general population. These mutations, in addition to the LA variant, are included in GAL14 / Galactosemia Gene Analysis (14-Mutation Panel) and in GCT / Galactosemia Reflex, Blood. See Galactosemia Testing Algorithm in Special Instructions for additional information. Refer to Galactosemia: Current Testing Strategy and Aids for Test Selection, Mayo Medical Laboratories Communique 2005 May;30(5) for more information regarding diagnostic strategy.

**Useful For:** Second-tier test for confirming a diagnosis of galactosemia (indicated by enzymatic
testing or newborn screening) Carrier testing family members of an affected individual of known

genotype (has mutations included in the panel) Resolution of Duarte variant and Los Angeles (LA)

variant genotypes

**Interpretation:** An interpretative report will be provided. Results should be interpreted in the context

of biochemical results.

**Reference Values:**

An interpretive report will be provided.


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**Galactosemia Reflex, Blood**

**Clinical Information:** Galactosemia is an autosomal recessive disorder that results from a deficiency

of 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate

uridyltransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase

(GALE). GALT deficiency is the most common cause of galactosemia and is often referred to as classic

galactosemia. The complete or near-complete deficiency of GALT enzyme is life threatening if left

untreated. Complications in the neonatal period include failure to thrive, liver failure, sepsis, and death;

even with survival, long-term intellectual disability can occur. Galactosemia is treated by a

galactose-restricted diet, which allows for rapid recovery from the acute symptoms and a generally good

prognosis. Despite adequate treatment from an early age, individuals with galactosemia remain at

increased risk for developmental delays, speech problems, and abnormalities of motor function. Females

with galactosemia are at increased risk for premature ovarian failure. Based upon reports by newborn

screening programs, the frequency of classic galactosemia in the United States is approximately 1 in

30,000, although literature reports range from 1 in 10,000 to 1 in 60,000 live births.

Galactose-1-phosphate (Gal-1-P) accumulates in the erythrocytes of patients with galactosemia. The

quantitative measurement of Gal-1-P is useful for monitoring compliance with dietary therapy. Gal-1-P is

thought to be the causative factor for development of liver disease in these patients and, because of this,

patients should maintain low levels and be monitored on a regular basis. Duarte-variant galactosemia

(compound heterozygosity for the Duarte mutation, N314D, and a classic mutation) is generally

associated with higher levels of enzyme activity (5%-20%) than classic galactosemia (<5%); however,

this may be indistinguishable by newborn screening assays. Typically, individuals with Duarte-variant

galactosemia have a milder phenotype, but are also often treated with a low galactose diet during infancy.

The Los Angeles variant, which consists of N314D and a second mutation, L218L, is associated with

higher levels of GALT enzyme activity than the Duarte-variant allele. Newborn screening for

galactosemia is performed in all 50 US states, though the method by which potentially affected

individuals are detected varies from state to state and may include the measurement of total galactose

(galactose and Gal-1-P) and/or determining the activity of the GALT enzyme. The diagnosis of

galactosemia is established by follow-up quantitative measurement of GALT enzyme activity. If enzyme

levels are indicative of carrier or affected status, molecular testing for common GALT mutations may be

performed. If 1 or both disease-causing mutations are not detected by targeted mutation analysis and

biochemical testing has confirmed the diagnosis of galactosemia, sequencing of the GALT gene is

available to identify private mutations. See Galactosemia Testing Algorithm in Special Instructions for

additional information.

**Useful For:** Preferred test for diagnosis, carrier detection, and determination of genotype of

galactose-1-phosphate uridyltransferase deficiency, the most common cause of galactosemia

Differentiating Duarte variant galactosemia from classic galactosemia Confirming results of newborn

screening programs

**Interpretation:** The laboratory provides an interpretation of the results, including

galactose-1-phosphate uridyltransferase enzyme activity and genotype, if necessary. This interpretation

provides an overview of the results and their significance, a correlation to available clinical information,
elements of differential diagnosis, and recommendations for additional testing. Any specimen where enzyme activity is less than 24.5 nmol/h/mg of hemoglobin will be analyzed for the presence of 14 mutations associated with classic galactosemia, as well as the 2 variants (Duarte and Los Angeles). See Galactosemia Reflex Algorithm in Special Instructions for testing algorithm and additional information. The GALT gene maps to 9p13. Several disease-causing mutations are common in patients with classic galactosemia (G/G genotype). The most frequently observed is the Q188R classic mutation. This mutation accounts for 60% to 70% of classical galactosemia alleles. The S135L mutation is the most frequently observed mutation in African Americans and accounts for approximately 50% of the mutant alleles in this population. The K285N mutation is common in those of eastern European descent and accounts for 25% to 40% of the alleles in this population. The L195P mutation is observed in 5% to 7% of classical galactosemia. The 5-kb deletion is common in individuals of Ashkenazi Jewish descent. The Duarte mutation (N314D and -119-116delGTCA) is observed in 5% of the general United States population. The rest of the mutations detected by this method (ie, D98N, S135L, T138M, M142K, F171S, Y209C, and Q344K) are all uncommon, but known to be recurrent in the general population. A high proportion (20%) of patients with classic galactosemia have a private mutation. Since our assay does not investigate for the presence of private mutations, when GG, DG, or NG genotype is predicted by enzymatic studies and the current panel does not identify a mutation, molecular sequencing may be indicated.

Reference Values:
> or =24.5 nmol/h/mg of hemoglobin


GALN3
70438

Galectin-3 (GAL3) Immunostain, Technical Component Only

Clinical Information: Galectin-3 is a member of the beta galactoside binding lectin family, and is involved in cellular adhesion. It is expressed by normal macrophages, neutrophils, mast cells. It is not expressed in normal or benign thyroid gland, but may be expressed in thyroid carcinoma.

Useful For: Aids in distinguishing normal and benign thyroid gland from thyroid carcinoma

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

Galectin-3, Serum

Clinical Information: Heart failure is a complex cardiovascular disorder with a variety of etiologies and heterogeneity with respect to the clinical presentation of the patient. Heart failure is significantly increasing in prevalence with an aging population and is associated with high short- and long-term mortality rate. Over 80% of patients diagnosed and treated for acute heart failure syndromes in the emergency department are readmitted within the forthcoming year, incurring costly treatments and therapies. The development and progression of heart failure is a clinically silent process until manifestation of the disorder, which typically occurs late and irreversibly into its progression. Mechanistically, heart failure, whether due to systolic or diastolic dysfunction, is thought to progress primarily through adverse cardiac remodeling and fibrosis in response to cardiac injury and/or stress. Galectin-3 is a biomarker that appears to be actively involved in both the inflammatory and fibrotic pathways that are thought to be involved. Galectin-3 is a carbohydrate-binding lectin whose expression is associated with inflammatory cells including macrophages, neutrophils, and mast cells. Galectin-3 has been linked to cardiovascular physiological processes including myofibroblast proliferation, tissue repair, and cardiac remodeling in the setting of heart failure. Concentrations of galectin-3 have been used to predict adverse remodeling after a variety of cardiac insults.

Useful For: An aid in prognosis for patients diagnosed with heart failure Risk-stratification of heart failure patients An early indication of treatment failure and as a therapeutic target

Interpretation: Clinically, galectin-3 concentrations may be categorized into 3 risk categories, substantiated by results from several large chronic heart failure studies:(2-4) < or =17.8 ng/mL (low risk) 17.9-25.9 ng/mL (intermediate risk) >25.9 ng/mL (higher risk) Results should be interpreted in the context of the individual patient presentation. Elevated galectin-3 results indicate an increased risk for adverse outcomes and signal the presence of galectin-3-mediated fibrosis and adverse remodeling. Once galectin-3 concentrations are elevated they are relatively stable over time in the absence of intervention. Knowledge of a heart failure patient's galectin-3 results may assist in risk stratification and lead to more aggressive management. There are no specific galectin-3 inhibitors available at this time and heart failure patients with elevated galectin-3 concentrations should be treated and monitored according to established guidelines. Angiotensin receptor blockers (ARBs) and aldosterone antagonists are thought to be particularly effective. A large multicenter, prospective, observational study was conducted to derive the reference intervals for galectin-3 that included 1,092 subjects between the ages of 55 and 80 years without any known cardiac disease (520 males, 572 females).(5) The 97.5th percentile of galectin-3 in that cohort was 22.1 ng/mL. Individuals with concentrations >22.1 ng/mL had a significant association with mortality and New York Heart Association (NYHA) classification. However, this was an older population and definitive evidence of cardiac disease was not documented.

Reference Values:
<24 months: not established
2-17 years: < or =25.0 ng/mL
> or =18 years: < or =22.1 ng/mL

Clinical Information: Classic galactosemia is an autosomal recessive disorder of galactose metabolism caused by mutations in the galactose-1-phosphate uridyltransferase (GALT) gene. The complete or near complete deficiency of the GALT enzyme is life threatening. If left untreated, complications include liver failure, sepsis, mental retardation, and death. Galactosemia is treated by a galactose-free diet, which allows for rapid recovery from the acute symptoms and a generally good prognosis. Despite adequate treatment from an early age, children with galactosemia remain at increased risk for developmental delays, speech problems, and abnormalities of motor function. Females with galactosemia are at increased risk for premature ovarian failure. The prevalence of classic galactosemia is approximately 1 in 30,000. Duarte variant galactosemia (compound heterozygosity for the Duarte variant, N314D, and a classic mutation) is generally associated with higher levels of GALT activity (5%-20%) than classic galactosemia (<5%); however, this may be indistinguishable by newborn screening assays. Typically, individuals with Duarte variant galactosemia have a milder phenotype, but are often treated with a low galactose diet during infancy. The LA variant, consisting of N314D and a second change, L218L, is associated with higher levels of GALT activity than the Duarte variant alone. Newborn screening, which identifies potentially affected individuals by measuring total galactose (galactose and galactose-1-phosphate) and/or determining the activity of the GALT enzyme, varies from state to state. The diagnosis of galactosemia is established by follow-up quantitative measurement of GALT activity. If enzyme activity levels are indicative of carrier or affected status, molecular testing for common GALT mutations may be performed. If 1 or both disease-causing mutations are not detected by targeted mutation analysis and biochemical testing has confirmed the diagnosis of galactosemia, sequencing of the GALT gene is available to identify private mutation(s). The GALT gene maps to 9p13. More than 180 mutations have been identified in the GALT gene. Several disease-causing mutations are common in patients with classic galactosemia (G/G genotype). The most frequently observed is the Q188R mutation. This mutation accounts for 60% to 70% of classic galactosemia alleles. The S135L mutation is the most frequently observed mutation in African Americans and accounts for approximately 50% of the mutant alleles in this population. The K285N mutation is common in those of eastern European descent and accounts for 25% to 40% of the alleles in this population. The L195P mutation is observed in 5% to 7% of classic galactosemia. The Duarte variant (N314D) is found in 5% of the general United States population. The above mutations, plus the LA variant, are included in GCT / Galactosemia Reflex, Blood, which is the preferred test for the diagnosis of galactosemia or for follow-up to positive newborn screening results. These mutations are also included in GAL14 / Galactosemia Gene Analysis (14-Mutation Panel). Full sequencing of the GALT gene can be useful for the identification of mutations when 1 or no mutations are found with these tests in an individual with demonstrated GALT activity deficiency. Full sequencing of the GALT gene identifies over 95% of the sequence variants in the coding region and splice junctions. See Galactosemia Testing Algorithm in Special Instructions for additional information.

Useful For: Identifying mutations in individuals who test negative for the common mutations and who have a biochemical diagnosis of galactosemia or galactose-1-phosphate uridyltransferase activity levels indicative of carrier status

Interpretation: All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.

**Clinical Information:** Hemoglobin F (Hb F) is the dominant hemoglobin at birth but is gradually replaced by adult hemoglobin (Hb A) during the year after birth (normal value ≤ 1% of total hemoglobin after age 2). Increased Hb F levels may continue after the neonatal period and into adulthood for various reasons. Genetic causes include deletional and nondeletional forms of hereditary persistence of fetal hemoglobin (HPFH) and delta-beta thalassemia mutations. Over 100 mutations have been described in the gamma genes and, if detectable, the protein expression will vary over time according to the overall Hb F expression. Gamma globin mutations can manifest either as a quantitative (gamma thalassemia or nondeletional HPFH) or a qualitative (gamma variant) abnormality. Nondeletional HPFH mutations frequently modulate the expected severity of sickling disorders due to the inhibitory properties of Hb F on sickle formation. Many gamma chain variants are benign, although some, such as unstable, high- and low-oxygen affinity, or M hemoglobin variants, cause hemolytic anemia/hyperbilirubinemia, erythrocytosis, cyanosis, and methemoglobinemia, respectively. The percentages of gamma variants will vary according to if they are present on the HBG1 or HBG2 genes, as these genes are differentially expressed depending on the age of the patient. Symptoms due to gamma variants are expected to decrease along with the normal decrease in Hb F and therefore most resolve after the first 6 months of life.

**Useful For:** An adjunct in the interpretation of hemoglobin electrophoresis results Evaluation for suspected gamma variants or nondeletional hereditary persistence of fetal hemoglobin (HPFH) Assess for unstable gamma chain variants (there are occasionally newborns who are jaundiced at birth, often requiring phototherapy, in which all other tests for causes of hemolysis are unrevealing)

**Interpretation:** An interpretive report will be provided and will include specimen information, assay information, and whether the specimen was positive for any mutations in the gene. If positive, the mutation will be correlated with clinical significance, if known.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
low-oxygen affinity, or M hemoglobin variants, cause hemolytic anemia/hyperbilirubinemia, erythrocytosis, cyanosis, and methemoglobinemia, respectively. The percentages of gamma variants will vary according to if they are present on the HBG1 or HBG2 genes, as these genes are differentially expressed depending on the age of the patient. Symptoms due to gamma variants are expected to decrease along with the normal decrease in Hb F and, therefore, most resolve after the first 6 months of life.

**Useful For:** Evaluates for the following in an algorithmic process for the HAEVP / Hemolytic Anemia Evaluation; HBELC / Hemoglobin Electrophoresis Cascade, Blood; MEVP / Methemoglobinemia Evaluation; REVE / Erythrocytosis Evaluation; THEVP / Thalassemia and Hemoglobinopathy Evaluation: -Evaluation for suspected gamma variants or nondeletional hereditary persistence of fetal hemoglobin (HPFH) Assess for unstable gamma chain variants (there are occasionally newborns who are jaundiced at birth, often requiring phototherapy, in which all other tests for causes of hemolysis are unrevealing)

**Interpretation:** An interpretive report will be provided and will include specimen information, assay information, and whether the specimen was positive for any mutations in the gene. If positive, the mutation will be correlated with clinical significance, if known.

**Reference Values:**
Only orderable as a reflex. For more information see:
- HAEVP / Hemolytic Anemia Evaluation
- HBELC / Hemoglobin Electrophoresis Cascade, Blood
- MEVP / Methemoglobinemia Evaluation
- REVE / Erythrocytosis Evaluation
- THEVP / Thalassemia and Hemoglobinopathy Evaluation

**Clinical References:**

**Gamma-Glutamyltransferase (GGT), Serum**

**Clinical Information:** Gamma-glutamyltransferase (GGT) is primarily present in kidney, liver, and pancreatic cells. Small amounts are present in other tissues. Even though renal tissue has the highest level of GGT, the enzyme present in the serum appears to originate primarily from the hepatobiliary system, and GGT activity is elevated in any and all forms of liver disease. It is highest in cases of intra- or posthepatic biliary obstruction, reaching levels some 5 to 30 times normal. GGT is more sensitive than alkaline phosphatase (ALP), leucine aminopeptidase, aspartate transaminase, and alanine aminotransferase in detecting obstructive jaundice, cholangitis, and cholecystitis; its rise occurs earlier than with these other enzymes and persists longer. Only modest elevations (2-5 times normal) occur in infectious hepatitis, and in this condition, GGT determinations are less useful diagnostically than are measurements of the transaminases. High elevations of GGT are also observed in patients with either primary or secondary (metastatic) neoplasms. Elevated levels of GGT are noted not only in the sera of patients with alcoholic cirrhosis but also in the majority of sera from persons who are heavy drinkers. Studies have emphasized the value of serum GGT levels in detecting alcohol-induced liver disease. Elevated serum values are also seen in patients receiving drugs such as phenytoin and phenobarbital, and this is thought to reflect induction of new enzyme activity. Normal values are observed in various
muscle diseases and in renal failure. Normal values are also seen in cases of skeletal disease, children older than 1 year, and in healthy pregnant women-conditions in which ALP is elevated.

Useful For: Diagnosing and monitoring hepatobiliary disease, it is currently the most sensitive enzymatic indicator of liver disease. Ascertainment whether observed elevations of alkaline phosphatase are due to skeletal disease (normal gamma-glutamyltransferase: GGT) or reflect the presence of hepatobiliary disease (elevated GGT). A screening test for occult alcoholism

Interpretation: An elevation of gamma-glutamyltransferase (GGT) activity is seen in any and all forms of liver disease, although the highest elevations are seen in intra- or posthepatic biliary obstruction. Elevated values can also indicate alcoholic cirrhosis or individuals who are heavy drinkers. The finding of increased GGT and alkaline phosphatase (ALP) activity is consistent with hepatobiliary disease. The finding of normal GGT activity and increased ALP activity is consistent with skeletal disease.

Reference Values:
Males
0-11 months: <178 U/L
12 months-6 years: <21 U/L
7-12 years: <24 U/L
13-17 years: <43 U/L
> or =18 years: 8-61 U/L

Females
0-11 months: <178 U/L
12 months- 6 years: <21 U/L
7-12 years: <24 U/L
13-17 years: <26 U/L
> or =18 years: 5-36 U/L


FGHSP 58034  Gamma-Hydroxybutyric Acid (GHB), Serum/Plasma
Reference Values:
Reference Range: Negative

Screening threshold: 5.0 ug/mL

FGHSU 58036  Gamma-Hydroxybutyric Acid (GHB), Urine
Reference Values:
Reference Range: Negative

Screening threshold: 5.0 ug/mL

GANC 80140  Ganciclovir, Serum
Clinical Information: Ganciclovir, an analog of acyclovir, demonstrates inhibitory action against some viruses including herpes virus, cytomegalovirus, and HIV. Therapeutic ranges have not been well-established for ganciclovir; current ranges are based on typical values seen during ganciclovir therapy and do not correlate well to toxicity or outcome. Monitoring of ganciclovir serum concentrations may be most useful in guiding therapy in patients with renal dysfunction. Myelosuppression is the major dose-limiting side effect of ganciclovir. Valcyte (valganciclovir) is an oral prodrug of ganciclovir ester. It
is immediately converted to ganciclovir once it enters the bloodstream. The oral dose is designed to deliver ganciclovir equivalent to intravenous ganciclovir at 5 mg/kg.

**Useful For:** Monitoring patients on ganciclovir

**Interpretation:** Serum concentrations of ganciclovir do not correlate well to toxicity or efficacy. Peak and trough levels provided are representative of typical serum concentrations seen during therapy, but individual values must be interpreted in conjunction with the clinical status of the individual patient and the specific characteristics of the infecting microorganism.

**Reference Values:**
- **Trough:** 1.0-3.0 mcg/mL
- **Peak:** 3.0-12.5 mcg/mL

**Clinical References:**

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Ganglioside (Asialo-GM1, GM1, GM2, GD1a, GD1b, and GQ1b) Antibodies

**Interpretation:** Ganglioside antibodies are associated with diverse peripheral neuropathies. Elevated antibody levels to ganglioside-monosialic acid (GM1) and the neutral glycolipid, asialo-GM1 are associated with motor or sensorimotor neuropathies, particularly multifocal motor neuropathy. Anti-GM1 may occur as IgM (polyclonal or monoclonal) or IgG antibodies. These antibodies may also be found in patients with diverse connective tissue diseases as well as normal individuals. GD1a antibodies are associated with different variants of Guillain-Barre syndrome (GBS) particularly acute motor axonal neuropathy while GD1b antibodies are predominantly found in sensory ataxic neuropathy syndrome. Anti-GQ1b antibodies are seen in more than 80 percent of patients with Miller-Fisher syndrome and may be elevated in GBS patients with ophthalmoplegia. The role of isolated anti-GM2 antibodies is unknown. These tests by themselves are not diagnostic and should be used in conjunction with other clinical parameters to confirm disease.

**Reference Values:**
- **29 IV or less:** Negative
- **30 â€“ 50 IV:** Equivocal
- **51 â€“ 100 IV:** Positive
- **101 IV or greater:** Strong Positive

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Ganglioside Antibody Panel, Serum

**Clinical Information:** Peripheral neuropathies are a group of disorders that results from lesions on peripheral nerves. Patients with a peripheral neuropathy can have symptoms of weakness, sensory loss, and/or autonomic dysfunction. The causes of acquired peripheral neuropathies are varied, and include vitamin deficiencies, metabolic abnormalities, infections, malignancies (paraneoplastic disorders), and autoimmune diseases. A subset of the autoimmune-mediated peripheral neuropathies is associated with the presence of circulating autoantibodies that bind to specific gangliosides. Gangliosides are glycosphingolipids that contain sialic acid residues. Although present in the plasma membranes of many cell types, gangliosides are particularly abundant in neural tissue. Guillain-Barre syndrome is one class of autoimmune peripheral neuropathies, and comprises a spectrum of disorders including acute inflammatory demyelinating polyradiculoneuropathy, acute motor axonal neuropathy, and acute motor and sensory axonal neuropathy. This class of autoimmune neuropathies is generally characterized by an acute onset. Although the diagnosis of these disorders is based significantly on clinical evaluation and electrophysiologic studies, assessment of ganglioside antibodies, particularly against GM1, asialo GM1, and GD1b, can provide useful information. It is thought that the Guillain-Barre syndrome disorders are...
triggered by an infection, which results in production of infection-associated lipooligosaccharide-specific antibodies. These antibodies subsequently bind to endogenous gangliosides, due to molecular mimicry, which leads to immune-mediate damage to the peripheral nerves, ultimately resulting in the clinical symptoms associated with the disorders.(1)

**Useful For:** Supporting diagnosis of neurological diseases—primarily motor neuron disease and motor neuropathies

**Interpretation:** High titers (>1:2,000) have been found only in patients with multifocal motor neuropathy and not with motor neuron disease. About 30% to 50% of patients with these clinical syndromes or the pure motor variant of chronic inflammatory demyelinating polyneuropathy have increased antibody titers. Increased antibody titers, therefore, appear to be a specific but not sensitive marker of those related disorders. Borderline elevation of titers against ganglioside epitopes may be seen in patients with motor neuron disease or motor neuropathy For IgG and IgM antibodies directed against monosialo GM1 and disialo GD1b, 99% of 182 age- and sex-stratified normal individuals had titers <1:1,000; 99% of 121 patients with well-defined motor neuron disease had titers <1:2,000; and all patients with titers >1:2,000 had motor neuropathy.

**Reference Values:**
- IgG monosialo GM1: 1:500
- IgM monosialo GM1: 1:1,000
- IgG asialo GM1: 1:4,000
- IgM asialo GM1: 1:4,000
- IgG disialo GD1b: 1:1,000
- IgM disialo GD1b: 1:1,000 Borderline Ranges
- IgG monosialo GM1: =1:1,000
- IgM monosialo GM1: =1:2,000
- IgG asialo GM1: =1:8,000
- IgM asialo GM1: No borderline range (normal: < or =4,000)
- IgG disialo GD1b: No borderline range (normal: < or =1,000)
- IgM disialo GD1b: No borderline range (normal: < or =1,000)

**Abnormal Results:**
- IgG monosialo GM1: >1:1,000
- IgM monosialo GM1: >1:2,000
- IgG asialo GM1: >1:8,000
- IgM asialo GM1: >1:4,000
- IgG disialo GD1b: >1:1,000
- IgM disialo GD1b: >1:1,000


FGQ1B  Ganglioside GQ1b Antibody (IgG), EIA
FGARG

**Reference Values:**
Less than 1:100 titer

**Garlic IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

GARL

**Garlic, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69 Equivocal</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49 Positive</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4 Positive</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9 Strongly positive</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9 Strongly positive</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive Reference values apply to all ages.</td>
<td></td>
</tr>
</tbody>
</table>
**GASTN 70439**

**Gastrin Immunostain, Technical Component Only**

**Clinical Information:** Gastrin is a polypeptide hormone produced and secreted by G cells in the antral mucosa of the stomach and in the duodenum and upper jejunum. The hormone is a potent stimulant of acid secretion and also increases gastric motility. Gastrin staining can identify G cells in the antral stomach and help characterize some islet cell tumors and other neuroendocrine tumors.

**Useful For:** Aids in the characterization of islet cell tumors and endocrine tumors of the gastrointestinal tract

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**GAST 8512**

**Gastrin, Serum**

**Clinical Information:** Gastrin is a peptide hormone produced by mucosal G cells of the gastric antrum. It is synthesized as preprogastrin, cleaved to progastrin, which undergoes several posttranslational modifications, in particular sulfation, and is finally processed into the mature 34-amino acid, gastrin-34. Gastrin-34 may be cleaved further into the shorter 17-amino acid, gastrin-17. Either may be secreted as a c-terminal amidated or unamidated isoform. A number of additional, smaller gastrin fragments, as well as gastrin molecules with atypical posttranslational modifications (eg, absent sulfation), may also be secreted in small quantities. Gastrin half-life is short, 5 minutes for amidated gastrin-17, and 20 to 25 minutes for amidated gastrin-34. Elimination occurs through peptidase cleavage and renal excretion. Gastrin-17 I (nonsulfated form) and gastrin-17 II (sulfated) appear equipotent. Their biological effects are chiefly associated with the amidated isoforms and consist of promotion of gastric epithelial cell proliferation and differentiation to acid-secreting cells, direct promotion of acid secretion, and indirect stimulation of acid production through histamine release. In addition, gastrin stimulates gastric motility and release of pepsin and intrinsic factor. Most gastrin isoforms with atypical posttranslational modifications and most small gastrin fragments display reduced or absent bioactivity. This assay measures predominately gastrin-17. Larger precursors and smaller fragments have little or no cross-reactivity in the assay. Intraluminal stomach pH is the main factor regulating gastrin production and secretion. Rising gastric pH levels result in increasing serum gastrin levels, while falling pH levels are associated with mounting somatostatin production in gastric D cells. Somatostatin, in turn, downregulates gastrin synthesis and release. Other weaker factors that stimulate gastrin secretion are gastric distention, protein-rich foods, and elevated secretin or serum calcium levels. Serum gastrin levels may also be elevated in gastric distention due to gastric outlet obstruction, and in a variety of conditions that lead to real or functional gastric hypo- or
achlorhydria (gastrin is secreted in an attempted compensatory response to achlorhydria). These include atrophic gastritis with or without pernicious anemia, a disorder characterized by destruction of acid-secreting (parietal) cells of the stomach; gastric dumping syndrome; and surgically excluded gastric antrum. In atrophic gastritis, the chronic cell-proliferative stimulus of the secondary hypergastrinemia may contribute to the increased gastric cancer risk observed in this condition. Gastrin levels are pathologically increased in gastrinoma, a type of neuroendocrine tumor that can occur in the pancreas (20%-40%) or in the duodenum (50%-70%). The triad of nonbeta islet cell tumor of the pancreas (gastrinoma), hypergastrinemia, and severe ulcer disease is referred to as the Zollinger-Ellison syndrome. Over 50% of gastrinomas are malignant and can metastasize to regional lymph nodes and the liver. About 25% of gastrinomas occur as part of the multiple endocrine neoplasia type 1 (MEN 1) syndrome and are associated with hyperparathyroidism and pituitary adenomas. These MEN 1-associated tumors have been observed to occur at an earlier age than sporadic tumors and often follow a more benign course. Basal and secretin-stimulated serum gastrin measurements are the best laboratory tests for gastrinoma.

**Useful For:** Investigation of patients with achlorhydria or pernicious anemia Investigation of patients suspected of having Zollinger-Ellison syndrome Diagnosis of gastrinoma

**Interpretation:** Achlorhydria is the most common cause of elevated serum gastrin levels. The most common cause for achlorhydria is treatment of gastroduodenal ulcers, nonulcer dyspepsia, or gastroesophageal reflux with proton pump inhibitors (substituted benzimidazoles, eg, omeprazole). Other causes of hypo- and achlorhydria include chronic atrophic gastritis with or without pernicious anemia, gastric ulcer, gastric carcinoma, and previous surgical or traumatic vagotomy. If serum B12 levels are significantly low (<150 ng/L), even if the intrinsic factor blocking antibody tests are negative, a serum gastrin level above the reference range makes it likely the patient is nonetheless suffering from pernicious anemia. Hypergastrinemia with normal or increased gastric acid secretion is suspicious of a gastrinoma (Zollinger-Ellison syndrome). Gastrin levels less than 100 pg/mL are observed so uncommonly in untreated gastrinoma patients with intact upper gastrointestinal anatomy as to virtually exclude the diagnosis. The majority (>60%) of patients with gastrinoma have very significantly elevated serum gastrin levels (>400 pg/mL). Levels above 1,000 pg/mL in a gastric- or duodenal-ulcer patient without previous gastric surgery, on no drugs, who has a basal gastric acid output of greater than 15 mmol/hour (>5 mmol/hour in patients with prior acid-reducing surgery) are considered diagnostic of gastrinoma. If there are any doubts about gastric acid output, an infusion of 0.1 N HCl into the stomach reduces the serum gastrin in patients with achlorhydria, but not in those with gastrinoma. Other conditions that may be associated with hypergastrinemia in the face of normal or increased gastric acid secretion include gastric and, rarely, duodenal ulcers, gastric outlet obstruction, bypassed gastric antrum, and gastric dumping. Occasionally, diabetes mellitus, autonomic neuropathy with gastroparesis, pheochromocytoma, rheumatoid arthritis, thyrotoxicosis, and paraneoplastic syndromes can also result in hypergastrinemia with normal acid secretion. None of these conditions tends to be associated with fasting serum gastrin levels above 400 pg/mL, and levels above 1,000 pg/mL are virtually never observed. Several provocative tests can be used to distinguish these patients from individuals with gastrinomas. Patients with gastrinoma who have normal or only mildly to modestly increased fasting serum gastrin levels, respond with exaggerated serum gastrin increases to intravenous infusions of secretin or calcium. Because of its greater safety, secretin infusion is preferred. The best validated protocol calls for a baseline fasting gastrin measurement, followed by an injection of 2 clinical units of secretin per kg body weight (0.4 microgram/kg) over 1 minute and further serum gastrin specimens at 5-, 10-, 15-, 20-, and 30-minutes postinjection. A peak gastrin increase of more than 200 pg/mL above the baseline value has greater than 85% sensitivity and near 100% specificity for gastrinoma. Secretin or calcium infusion tests are not carried out in the clinical laboratory, but are usually performed at gastroenterology or endocrine testing units under the supervision of a physician. They are progressively being replaced (or supplemented) by imaging procedures, particularly duodenal and pancreatic endoscopic ultrasound. All patients with confirmed gastrinoma should be evaluated for possible multiple endocrine neoplasia type 1 (MEN 1), which is the underlying cause in approximately 25% of cases. If clinical, biochemical, or genetic testing confirms MEN 1, other family members need to be screened.

**Reference Values:**

<100 pg/mL

There is no evidence that fasting serum gastrin levels differ between adults and children. Although 8-hour fasts are difficult or impossible to enforce in small children, serum gastrin levels after shorter
fasting periods (3-8 hours) may be 50% to 60% higher than the 8-hour fasting value.

For SI unit Reference Values, see

**Clinical References:**

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**Gastrointestinal Pathogen Panel, PCR, Feces**

**Clinical Information:** Acute diarrheal syndromes are usually self-limiting, but may be complicated by dehydration, vomiting, and fever. Diagnostic testing and treatment may be required in some instances. Many bacterial enteric infections in the United States originate within the food supply chain. According to the CDC, in 2012 there were 19,531 laboratory-confirmed cases of infection with pathogens potentially transmitted through food in the United States. The number of infections, by pathogen, were as follows: Salmonella species (7,800), Campylobacter species (6,793), Shigella species (2,138), Cryptosporidium species (1,234), Shiga toxin-producing Escherichia coli non-O157 (551), Shiga toxin-producing E coli O157 (531), Vibrio species (193), Yersinia species (155), and Cyclospora cayetanensis (15). Giardia may also be transmitted through ingestion of contaminated food and water. There were 15,178 cases of giardiasis reported to the CDC in 2012. Since the clinical presentation may be very similar to many of these bacterial, viral, and parasitic pathogens, laboratory testing is required for definitive identification of the causative agent. Rapid multiplex panel detection of the most common agents of bacterial, viral, and parasitic enteric infections directly from stool specimens is sensitive, specific, and provides same-day results, obviating the need for culture, antigen testing, microscopy, or individual nucleic acid amplification tests. See Parasitic Investigation of Stool Specimens Algorithm and Laboratory Testing for Infectious Causes of Diarrhea in Special Instructions for other diagnostic tests that may be of value in evaluating patients with diarrhea.

**Useful For:**
- Rapid detection of gastrointestinal infections caused by: Campylobacter species
  - Campylobacter jejuni/Campylobacter coli/Campylobacter upsaliensis
  - Plesiomonas shigelloides
  - Salmonella species
  - Vibrio species (Vibrio parahaemolyticus, Vibrio vulnificus, Vibrio cholerae)
  - Vibrio cholerae
  - Yersinia species
  - Enteropathogenic Escherichia coli (EPEC)
  - Enterotoxigenic E coli (ETEC)
  - Shiga toxin - E coli O157
  - Shigella/Enteroinvasive E coli (EIEC)
  - Cryptosporidium species
  - Cyclospora cayetanensis
  - Entamoeba histolytica
  - Giardia
  - Adenovirus F 40/41
  - Astrovirus
  - Norovirus GI/GII
  - Rotavirus
  - Sapovirus

**Interpretation:** A negative result should not rule-out infection in patients with a high pretest probability for gastrointestinal infection. The assay does not test for all potential infectious agents of diarrheal disease. Positive results do not distinguish between a viable or replicating organism and the presence of a nonviable organism or nucleic acid, nor do they exclude the potential for coinfection by organisms not contained within the panel. Results of the panel are intended to aid in the diagnosis of illness and are meant to be used in conjunction with other clinical and epidemiological findings. In some cases, there may be local public health requirements that impact Mayo Medical Laboratories (MML) clients and require additional testing on specimens with positive results from this panel. Clients should familiarize themselves with local requirements. MML recommends that clients retain an aliquot of each specimen submitted for this test to perform additional testing themselves, as needed. If necessary, selected add-on tests can be performed by MML at an additional charge, as detailed below. Call MML within 96 hours of specimen collection to request supplemental testing for positive GIP test results: Gastrointestinal Pathogen Panel Positive for Client Action Campylobacter species Salmonella species

- Shigella/Enteroinvasive E coli
- Yersinia species

Request add on test: STL / Enteric Pathogens Culture, Stool (for the Shigella/Enteroinvasive E coli target, the culture will assess for Shigella species only)
Vibrio species Request add on test: VIBC / Vibrio Culture, Stool Shiga toxin-producing E coli E coli O157 Request aliquot of stool be returned to client for submission to their state or city department of health MML will report such culture results to the client for Enteric Pathogens Culture or Vibrio Culture when ordered. If cultures are positive and the client is in need of the isolated organism (eg, Campylobacter, Salmonella, Shigella, Yersinia, or Vibrio species) for submission to a public health laboratory, the client needs to call MML and request that the isolates be returned to them (the client). The client will be responsible for submitting the isolates to the appropriate public health department. Positive culture results will also be reported via the Electronic Clinical Laboratory Reporting System (ECLRS). Alternatively (not preferred), clients who want a patient specimen returned from MML should call MML as soon as possible and at the latest within 96 hours of specimen collection to request that MML return an aliquot of the submitted specimen to them. Clients will be responsible for submitting specimens to appropriate public health departments.

Reference Values:
Negative (for all targets)

Clinical References:

GATA3

GATA Binding Protein 3 Immunostain, Technical Component Only

Clinical Information: GATA-binding protein 3 (GATA3) is a transcription factor of the GATA family. GATA3 is involved in the regulation of development and differentiation of a variety of human tissues including T cells, skin, kidney, mammary gland, and the central nervous system. GATA3 has been shown to be a useful in the characterization of carcinomas, including primary bladder and breast carcinomas, and some types of mesenchymal and neuroectodermal tumors (ie, paragangliomas).

Useful For: Characterizing carcinomas, including primary bladder and breast carcinomas, and some types of mesenchymal and neuroectodermal tumors

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


GATA-Binding Protein 2 (GATA2) Comprehensive Gene Sequencing

Clinical Information: GATA-binding protein 2 (GATA2) deficiency is emerging as the second most common primary immunodeficiency (PID) or inborn error of immunity in adults, after common variable immunodeficiency (CVID). There is a spectrum of clinical presentations associated with GATA2 deficiency, including severe viral infections (e.g., human papillomavirus [HPV] warts), fungal infections, bacterial infections (e.g., atypical mycobacterial infections such as nontuberculous mycobacterial infections [NTM] or mycobacterium avium complex [MAC]), myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and Emberger syndrome (primary lymphedema with MDS). Other clinical phenotypes of GATA2 deficiency may include aplastic anemia, pulmonary alveolar proteinosis (PAP), sensorineural hearing loss, neutropenia, and congenital lymphedema without MDS at diagnosis. Immunological phenotypes include dendritic cell, monocyte, CD4+ T cell, B and natural killer (NK) cell deficiencies. Also, the loss of a specific NK-cell subset, CD56 bright NK cells, has been reported in these patients. GATA2 deficiency was first described in 2011 as being associated with either MonoMAC (monocytopenia and mycobacterial infection) syndrome or DCML deficiency (dendritic cell, monocyte, B and NK cell lymphocyte deficiency). GATA2 is a zinc finger transcription factor, involved in the generation and function of hematopoietic stem cell progenitors and, therefore, affects several of the subsequent cell lineages. GATA2 deficiency is a disease of haploinsufficiency, and most germline variants appear to arise de novo (spontaneously) but are then transmitted in an autosomal dominant manner. Standard genotype-phenotype correlations are difficult to make, as there is considerable clinical heterogeneity and the age of presentation varies from early childhood to late in adult life. Additionally, there may be a role for environmental factors triggering certain infectious manifestations. There has been incomplete penetration (not every individual with a mutation has a clinical phenotype) observed with GATA2 deficiency as well as variable expressivity (different clinical presentations for the same genetic mutation). The genetic alterations observed in GATA2 are heterogeneous, and include missense variants, nonsense variants, and variants in the regulatory region of intron 5, in-frame deletions involving the C-terminal zinc finger domain, frameshift mutations variants, and large deletions. The latter are associated with null alleles, while regulatory mutations variants have been observed in the enhancer region of intron 5. Somatic mutations variants in ASXL1 have been reported in GATA2 patients and have been postulated to be associated with transformation to myeloid leukemia. The definitive treatment for GATA2 deficiency is hematopoietic cell transplantation (HCT). Additionally, systemic use of interferon-alpha may be helpful in patients with NK cell deficiency who have recurrent or severe HPV or herpes virus infections. Also, prophylactic antibiotics may be needed or mandated in the nontransplanted patient. The pulmonary alveolar proteinosis observed in GATA2 deficiency is in the context of negative results for anti-GM-CSF autoantibodies has been shown to improve after HCT and suggests correction of alveolar macrophage function. Early genetic diagnosis of GATA2 deficiency is critical in determining strategies for managing the disease considering the broad clinical spectrum. Genetic diagnosis by confirmation of a pathogenic GATA2 variant may also aid in family counseling and screening.

Useful For: A comprehensive evaluation of the GATA2 gene in patients with clinical or immunological symptoms suggestive of GATA-binding protein 2 (GATA2) deficiency Screening family members of patients with confirmed GATA2 deficiency

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Unless reported or predicted to cause disease, alterations found deep in the intron or alterations that do not result in an amino acid substitution are not reported. A list of common (presumed benign) GATA2 variants identified for this patient are available from the lab upon request.

Reference Values:
An interpretive report will be provided.

**Clinical References:**

**GATA-Binding Protein 3 Immunostain, Bone Marrow, Technical Component Only**

**Clinical Information:** GATA-binding protein 3 (GATA3) is a transcription factor of the GATA family. GATA3 is involved in the regulation of development and differentiation of a variety of human tissues including T cells, skin, kidney, mammary gland, and the central nervous system. GATA3 has been shown to be a useful in the characterization of carcinomas, including primary bladder and breast carcinomas, and some types of mesenchymal and neuroectodermal tumors (ie, paragangliomas).

**Useful For:** Characterizing carcinomas, including primary bladder and breast carcinomas, and some types of mesenchymal and neuroectodermal tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
Gaucher Disease, Full Gene Analysis

Clinical Information: Gaucher disease is a relatively rare lysosomal storage disorder resulting from a deficiency of acid beta-glucocerebrosidase. Reduced or absent activity of this enzyme results in accumulation of its substrate in lysosomes, interfering with cell function. There are 3 major types of Gaucher disease: nonneuropathic (type 1), acute neuropathic (type 2), and subacute neuropathic (type 3). In addition, there are 2 rare presentations of Gaucher disease: perinatal lethal form associated with skin abnormalities and nonimmune hydrops fetalis, and a cardiovascular form presenting with calcification of the aortic and mitral valves, mild splenomegaly, and corneal opacities. Gaucher disease demonstrates large clinical variability, even within families. Type 1 accounts for over 95% of all cases of Gaucher disease and is the presentation commonly found among Ashkenazi Jewish patients. The carrier rate of Gaucher disease in the Ashkenazi Jewish population is 1:18. There is a broad spectrum of disease in type 1 Gaucher disease, with some patients exhibiting severe symptoms and others very mild disease. Type 1 disease does not involve nervous system dysfunction; patients may display anemia, low blood platelet levels, massively enlarged livers and spleens, lung infiltration, and extensive skeletal disease. Type 2 is characterized by early-onset neurologic disease with rapid progression to death by 2 to 4 years of age. Type 3 may have early onset of symptoms, but generally a slower disease progression than type 2. Mutations in the GBA gene cause the clinical manifestations of Gaucher disease. Over 250 mutations have been reported to date. The N370S and L444P mutations have the highest prevalence in most populations. N370S is associated with type 1 Gaucher disease, and individuals with at least 1 copy of this mutation do not develop the primary neurologic disease seen in types 2 and 3. Conversely, L444P is associated with neurologic disease. Mutations in the GBA gene have also been reported to cause an increased risk for Parkinson disease. Alterations associated with Parkinson disease, but not Gaucher disease, are not routinely reported for patients under the age of 18, but are available upon request. For carrier screening of the general population, the recommended test is GAUP / Gaucher Disease, Mutation Analysis, GBA, which tests for the 8 most common GBA mutations. For diagnostic testing (ie, potentially affected individuals), enzyme testing (BGL / Beta-Glucosidase, Leukocytes) should be performed prior to mutation analysis. In individuals with abnormal enzyme activity and 1 or no mutations detected by a panel of common mutations, sequence analysis of the GBA gene should be utilized to detect private mutations.

Useful For: Confirmation of a diagnosis of Gaucher disease Carrier screening in cases where there is a family history of Gaucher disease, but an affected individual is not available for testing or disease-causing mutations have not been identified

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.

patients. The carrier rate of Gaucher disease in the Ashkenazi Jewish population is 1 in 18. Type 1 disease does not involve nervous system dysfunction; patients display anemia, low blood platelet levels, massively enlarged livers and spleens, lung infiltration, and extensive skeletal disease. The clinical variability in type 1 disease is large, with some patients exhibiting severe disease and others very mild disease. Eight GBA mutations, including the N370S mutation found most commonly in the Ashkenazi Jewish population, are included in this test: delta 55bp, V394L, N370S, IVS2+1, 84GG, R496H, L444P, and D409H. This testing panel provides a 95% detection rate for the Ashkenazi Jewish population and up to a 60% detection rate for the non-Ashkenazi Jewish population. Alternatively, full gene sequencing is available to evaluate for mutations in all coding regions and exon/intron boundaries of the GBA gene by ordering GBAZ / Gaucher Disease, Full Gene Analysis.

**Useful For:** Confirmation of a suspected clinical diagnosis of Gaucher disease Carrier testing for individuals of Ashkenazi Jewish ancestry or who have a family history of Gaucher disease Prenatal diagnosis of Gaucher disease in at-risk pregnancies

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**GCDFP-15 Immunostain, Technical Component Only**

**Clinical Information:** Immunohistochemical staining with the monoclonal antibody GCDFP-15 produces diffuse, granular cytoplasmic staining in apocrine sweat glands, normal breast epithelial cells, and breast carcinoma malignant cells. Other neoplasms expressing GCDFP-15 are extramammary Paget disease and carcinomas of the salivary glands, sweat glands, and prostate. A heterogeneous staining pattern, often with paranuclear enhancement, is usually obtained in breast carcinoma.

**Useful For:** Aids in the identification of extramammary Paget disease, carcinomas of the salivary glands, sweat glands, and prostate

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
Gelatin Porcine IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35–0.69 Low Positive 2 0.70–3.49 Moderate Positive 3 3.50–17.49 Positive 4 17.50–49.99 Strong Positive 5 50.00–99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

Gelatin, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<td>0</td>
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<tr>
<td>1</td>
<td>0.35-0.69</td>
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<td>5</td>
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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**Gelsolin (GSN) Gene, Full Gene Analysis**

**Clinical Information:** The systemic amyloidoses are a number of disorders of varying etiology characterized by extracellular protein deposition. The most common form is an acquired amyloidosis secondary to multiple myeloma or monoclonal gammopathy of unknown significance (MGUS) in which the amyloid is composed of immunoglobulin light chains. In addition to light chain amyloidosis, there are a number of acquired amyloidoses caused by the misfolding and precipitation of a wide variety of proteins. There are also hereditary forms of amyloidosis. The hereditary amyloidoses comprise a group of autosomal dominant, late-onset diseases that show variable penetrance. A number of genes have been associated with hereditary forms of amyloidosis including those that encode transthyretin, apolipoprotein AI, apolipoprotein AII, fibrinogen alpha chain, cystatin C, lysozyme, and gelsolin. Apolipoprotein AI, apolipoprotein AII, lysozyme, and fibrinogen amyloidosis present as non-neuropathic systemic amyloidosis, with renal dysfunction being the most prevalent manifestation. Gelsolin (GSN) amyloidosis (amyloidosis V) is characterized by corneal lattice dystrophy, cranial neuropathy, and skin changes. Peripheral neuropathy may be present but is typically mild. Like the other hereditary amyloidoses, it is an autosomal dominant disorder; however, homozygosity has been reported and is associated with accelerated renal disease. Due to the clinical overlap between the acquired and hereditary forms, it is imperative to determine the specific type of amyloidosis in order to provide an accurate prognosis and consider appropriate therapeutic interventions. Tissue-based, laser capture tandem mass spectrometry might serve as a useful test preceding gene sequencing to better characterize the etiology of the amyloidosis, particularly in cases that are not clear clinically.

**Useful For:** Diagnostic confirmation of amyloidosis V

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Gentamicin in Cerebrospinal Fluid (CSF)**

**Reference Values:**
Reference Range: Not Established

Units: ug/mL

**Gentamicin, Peak, Serum**

**Clinical Information:** Gentamicin is an antibiotic used to treat life-threatening blood infections caused by gram-negative bacilli, particularly Citrobacter freundii, Acinetobacter species, Enterobacter species, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia species. It is often used in combination with beta-lactam therapy. A gentamicin minimal inhibitory concentration (MIC) of less than or equal to 4 mcg/mL is considered susceptible for gram-negative bacilli. A MIC of less than or equal to 500 mcg/mL is considered synergistic when combined with appropriate antibiotics for treatment of serious enterococcal infections. Conventional
dosing of gentamicin is usually given 2 to 3 times per day by intravenous or intramuscular injections in
doses to achieve peak blood concentration between 3.0 and 12.0 mcg/mL depending on the type of
infections. Gentamicin also may be administered at higher doses (usually 5-7 mg/kg) once per day to
patients with good renal function (known as pulse dosing). Dosing amount or interval must be decreased
to accommodate for reduced renal function. Ototoxicity and nephrotoxicity are the primary toxicities
associated with gentamicin. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs.
Monitoring of serum levels and symptoms consistent with ototoxicity is important. For longer durations
of use, audiology/vestibular testing should be considered at baseline and periodically during therapy.

**Useful For:** Monitoring adequacy of drug clearance during gentamicin therapy

**Interpretation:** Goal levels depend on the type of infection being treated. Peak targets are generally
between 5.0 and 8.0 mcg/mL for less severe infections and 8.0 and 10.0 mcg/mL for severe infections.
Prolonged exposure to peak levels exceeding 12.0 mcg/mL may lead to toxicity.

**Reference Values:**
- **Peak:** 3.0-12.0 mcg/mL
- **Toxic peak:** >12.0 mcg/mL

**Clinical References:**
1. Hammett-Stabler CA, Johns T: Laboratory guidelines for monitoring of
2. Moyer TP: Therapeutic drug monitoring. In
Tietz Textbook of Clinical Chemistry, Fourth edition. Edited by CA Burtis, ER Ashwood, Philadelphia,
WB Saunders Company, 2006
Mayo Clinic Scientific Press and Informa Healthcare USA, 2008

GENTAMICIN, TROUGH, SERUM

**Clinical Information:** Gentamicin is an antibiotic used to treat life-threatening blood infections caused by gram-negative bacilli, particularly Citrobacter freundii, Acinetobacter species, Enterobacter species, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia species. It is often used in combination with beta-lactam therapy. A gentamicin minimal inhibitory concentration (MIC) of 4.0 mcg/mL or less is considered susceptible for gram-negative bacilli. A MIC of 500 mcg/mL or less is considered synergistic when combined with appropriate antibiotics for treatment of serious enterococcal infections. Conventional dosing of gentamicin is usually given 2 to 3 times per day by intravenous or intramuscular injections in doses to achieve peak blood concentration between 3.0 to 12.0 mcg/mL depending on the type of infection. Gentamicin also may be administered at higher doses (usually 5-7 mg/kg) once per day to patients with good renal function (known as pulse dosing). Dosing amount or interval must be decreased to accommodate for reduced renal function. Ototoxicity and nephrotoxicity are the primary toxicities associated with gentamicin. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs. Monitoring of serum levels and symptoms consistent with ototoxicity is important. For longer durations of use, audiology/vestibular testing should be considered at baseline and periodically during therapy.

**Useful For:** Monitoring adequacy of drug clearance during gentamicin therapy

**Interpretation:** Goal levels depend on the type of infection being treated. Goal trough levels should be less than 2.0 mcg/mL for conventional dosing. Prolonged exposure to trough levels exceeding 2.0 mcg/mL may lead to toxicity.

**Reference Values:**
- Therapeutic: <2.0 mcg/mL
- Toxic: >2.0 mcg/mL


GERMIL EPITHELIUM, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of IgE-mediated allergic reactions.
of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Germ Cell Tumor (GCT), Isochromosome 12p, FISH, Tissue**

**Clinical Information:** Germ cell tumors (GCT) comprise a heterogeneous group of solid neoplasms that arise in midline locations including the gonads, retroperitoneum, mediastinum, and central nervous system. GCT are categorized based upon their histologic differentiation and can be separated into 2 classes. Seminomatous GCT include seminoma of the testis, dysgerminoma of the ovaries, and germinoma of the brain. Nonseminomatous GCT include yolk sac tumor, embryonal carcinoma, choriocarcinoma, immature teratoma, and mixed forms. Due to the wide spectrum of histologic features observed in these tumors, distinction from non-GCT can be difficult. GCT are often very responsive to chemotherapy and have a better outcome relative to histologically similar malignancies. Thus, distinguishing GCT from non-GCT is critical to providing the appropriate treatment for the patient. Gain of the short arm of chromosome 12, most commonly as an isochromosome 12p[i(12p)], is a highly nonrandom chromosomal marker seen in a significant percentage of GCT. While i(12p) is not 100% specific for GCT, the literature indicates it has diagnostic and possible therapeutic relevance for patients with these tumors. Testing of i(12p) should be concomitant with histologic evaluation, and positive results may support the diagnosis of GCT.

**Useful For:** Supporting the diagnosis of germ cell tumors when used in conjunction with an anatomic pathology consultation

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the i(12p) probe set. A positive result is consistent with the diagnosis of a germ cell tumors (GCT). A negative result suggests that the i(12p) marker is not present, but does not exclude the diagnosis of a GCT.

**Reference Values:**

An interpretive report will be provided.

GCTH 70442

**Germinal Center B-cell Expressed Transcript 1 (GCET1)**

**Immunostain, Technical Component Only**

**Clinical Information:** Germinal center B-cell expressed transcript 1 (GCET1), is also known as Centerin and SERPIN9 (serine protease inhibitor). GCET1 is expressed in B cells in the germinal center of normal lymph node and tonsil tissues. Most follicular lymphomas strongly express GCET1. In addition, a proportion of diffuse large B-cell lymphomas (DLBCL) are positive. In the diagnosis of B-cell lymphomas, GCET1 can be useful in an immunohistochemical panel to assign a germinal center phenotype.

**Useful For:** Classification of lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


FGHTL 57902

**Ghrelin Total, Plasma**

**Reference Values:**

GHRELIN (Total): pg/mL

(Plasma)

Adult Reference Range(s)

Normal weight/control subjects: 520 - 700 pg/mL

Obese subjects prior to diet: 340 - 450 pg/mL

Levels:

8:00 am - 12:00 pm: Up to 420 pg/mL

6:00pm: Up to 480 pg/mL

Obese subjects post induced weight loss: 450 - 600 pg/mL

Levels:

8:00 am - 12:00 pm: Up to 575 pg/mL

6:00 pm: Up to 600 pg/mL

Obese subjects post gastric-bypass surgery: Up to 120 pg/mL

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 983
**Giant Ragweed, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
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**Giardia Antigen, Feces**

**Clinical Information:** Giardia lamblia (also known as G duodenalis, G intestinalis) is a flagellated protozoan parasite that can be found in contaminated natural streams, lakes, and surface water municipal reservoirs. Humans become infected when ingesting the environmentally resistant cysts in water, food, and by the fecal-oral route. G lamblia primarily infects the small intestine causing malodorous watery diarrhea and flatulence after attaching by their ventral sucker. Malabsorption and lactose intolerance may also occur. Giardiasis is the most common intestinal parasitic infection in the United States that is reported to the CDC and is a common cause of diarrhea in children (especially in day care centers), travelers, and campers. It is also responsible for waterborne epidemics. Although G lamblia may be seen using the microscopy-based stool parasitic exam (OAP / Parasitic Examination), this is an insensitive method for detection. Instead, detection of parasite antigen or DNA is recommended for optimal...
sensitivity. See Parasitic Investigation of Stool Specimens Algorithm and Laboratory Testing for Infectious Causes of Diarrhea in Special Instructions for other diagnostic tests that may be of value in evaluating patients with diarrhea.

**Useful For:** Sensitive screening for the detection of Giardia lamblia antigens present in stool specimens

**Interpretation:** A positive enzyme-linked immunosorbent assay (ELISA) indicates the presence in a stool specimen of Giardia lamblia antigens. As per the manufacturer, the assay has a sensitivity of 96%, specificity of 97%, and a positive predictive value of 95%. Interpretation of results should be correlated with patient symptoms and clinical picture.

**Reference Values:**
Negative

**Clinical References:**

**Ginger, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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GISTP 35342

GIST-Targeted Gene Panel by Next-Generation Sequencing, Tumor

Clinical Information: Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the United States Food and Drug Administration (FDA) for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Next-generation sequencing has recently emerged as an accurate, cost-effective method to identify mutations across numerous genes known to be associated with response or resistance to specific targeted therapies. This test is a single assay that uses formalin-fixed paraffin-embedded tissue to assess for common mutations in the KIT and PDGFRA genes known to be associated with gastrointestinal stromal tumors (GIST). The results of this test can be useful for assessing prognosis and guiding treatment of individuals with GIST. See Targeted Gene Regions Interrogated by Solid Tumor Targeted Cancer Gene Panel by Next Generation Sequencing in Special Instructions for details regarding the targeted gene regions identified by this test.

Useful For: Diagnosis and management of patients with gastrointestinal stromal tumors

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.


DGLDN 89031

Gliadin (Deamidated) Antibodies Evaluation, IgG and IgA, Serum

Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process that occurs in genetically susceptible individuals following ingestion of wheat, rye, or barley proteins. (1) The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. (1) Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and/or constipation. (2)
Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis.(3) Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma.(1,2) The disease is also associated with other clinical disorders including thyroiditis, type 1 diabetes mellitus, Down syndrome, and IgA deficiency.(1,3) Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population.(3) A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy.(1-3) Given the invasive nature and cost of the biopsy, serologic tests may be used to identify individuals with a high probability of having celiac disease. Because no single laboratory test can be relied upon completely to establish a diagnosis of celiac disease, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures. Celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies.(4) Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient.(2) The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. Testing for IgA and IgG antibodies to unmodified gliadin proteins is no longer recommended because of the low sensitivity and specificity of these tests for celiac disease; however, recent studies have identified specific B-cell epitopes on the gliadin molecule that, when deamidated by the enzyme tTG, have increased sensitivity and specificity for celiac disease.(5,6) The tests for deamidated gliadin antibodies, IgA and IgG, replace the older gliadin antibody tests, which have been discontinued at Mayo Clinic. The sensitivity and specificity of DGLDN / Gliadin (Deamidated) Antibodies Evaluation, IgG and IgA, Serum for untreated, biopsy-proven celiac disease were comparable to test TSTGP / Tissue Transglutaminase (tTG) Antibodies, IgA and IgG Profile, Serum in a study conducted at Mayo Clinic.(5) The treatment for celiac disease is maintenance of a gluten-free diet.(1-3) In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves. This is typically accompanied by an improvement in clinical symptoms. For evaluation purposes, all serologic tests ordered for the diagnosis of celiac disease should be performed while the patient is on a gluten-containing diet. Once a patient has initiated the gluten-free diet, serologic testing may be repeated to assess the response to treatment. In some patients, it may take up to 1 year for antibody titers to normalize. Persistently elevated results suggest poor adherence to the gluten-free diet or the possibility of refractory celiac disease.(1) See Celiac Disease Diagnostic Testing Algorithm in Special Instructions for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions. For your convenience, we recommend utilizing cascade testing for celiac disease. Cascade testing ensures that testing proceeds in an algorithmic fashion. The following cascades are available; select the appropriate one for your specific patient situation. Algorithms for the cascade tests are available in Special Instructions. - CDCOM / Celiac Disease Comprehensive Cascade: complete testing including HLA DQ - CDSP / Celiac Disease Serology Cascade: complete testing excluding HLA DQ - CDGF / Celiac Disease Gluten-Free Cascade: for patients already adhering to a gluten-free diet To order individual tests, see Celiac Disease Diagnostic Testing Algorithm in Special Instructions.

Useful For: Evaluating patients suspected of having celiac disease; this includes patients with symptoms compatible with celiac disease, patients with atypical symptoms, and individuals at increased risk of celiac disease Evaluating the response to treatment with a gluten-free diet

Interpretation: Positive test results for deamidated gliadin antibodies, IgA or IgG, are consistent with the diagnosis of celiac disease. Negative results indicate a decreased likelihood of celiac disease. Decreased levels of deamidated gliadin antibodies, IgA or IgG, following treatment with a gluten-free diet are consistent with adherence to the diet. Persistence of high levels of antibodies following dietary treatment suggest poor adherence to the diet or the presence of refractory disease. See Celiac Disease Diagnostic Testing Algorithm in Special Instructions for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions.
Gliadin (Deamidated) Antibody, IgA, Serum

Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process that occurs in genetically susceptible individuals following ingestion of wheat, rye, or barley proteins. The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and/or constipation. Other common manifestations of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma. Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population. A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy. Given the invasive nature and cost of the biopsy, serologic tests may be used to identify individuals with a high probability of having celiac disease. Because no single laboratory test can be relied upon completely to establish a diagnosis of celiac disease, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures. Celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies. Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. Testing for IgA and IgG antibodies to unmodified gliadin proteins is no longer recommended because of the low sensitivity and specificity of these tests for celiac disease; however, recent studies have identified specific B-cell epitopes on the gliadin molecule that, when deamidated by the enzyme tTG, have increased sensitivity and specificity for celiac disease. The tests for deamidated gliadin antibodies, IgA and IgG, replace the older gliadin antibody tests, which have been discontinued at Mayo Clinic. The sensitivity and specificity of DGLDN / Gliadin (Deamidated) Antibodies Evaluation, IgG and IgA, Serum for untreated, biopsy-proven celiac disease were comparable to test TSTGP / Tissue Transglutaminase (tTG) Antibodies, IgA and IgG Profile, Serum in a study conducted at Mayo Clinic. The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves. This is typically accompanied by an improvement in clinical symptoms. For evaluation purposes, all serologic tests ordered for the diagnosis of celiac disease should be performed while the patient is on a gluten-containing diet. Once a patient has initiated the gluten-free diet, serologic testing may be repeated to assess the response to treatment. In some patients, it may take up to 1 year for antibody titers to normalize. Persistently elevated results suggest poor adherence to the gluten-free diet or the possibility of refractory celiac disease.
Disease Diagnostic Testing Algorithm in Special Instructions for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions. For your convenience, we recommend utilizing cascade testing for celiac disease. Cascade testing ensures that testing proceeds in an algorithmic fashion. The following cascades are available; select the appropriate one for your specific patient situation. Algorithms for the cascade tests are available in Special Instructions. -DAGL / Celiac Disease Comprehensive Cascade: complete testing including HLA DQ -CDSP / Celiac Disease Serology Cascade: complete testing excluding HLA DQ -CDGF / Celiac Disease Gluten-Free Cascade: for patients already adhering to a gluten-free diet To order individual tests, see Celiac Disease Diagnostic Testing Algorithm in Special Instructions.

Useful For: Evaluating patients suspected of having celiac disease; this includes patients with symptoms compatible with celiac disease, patients with atypical symptoms, and individuals at increased risk of celiac disease Evaluating the response to treatment with a gluten-free diet

Interpretation: Positive test results for deamidated gliadin antibodies, IgA or IgG, are consistent with the diagnosis of celiac disease. Negative results indicate a decreased likelihood of celiac disease. Decreased levels of deamidated gliadin antibodies, IgA or IgG, following treatment with a gluten-free diet are consistent with adherence to the diet. Persistence of high levels of antibodies following dietary treatment suggest poor adherence to the diet or the presence of refractory disease. See Celiac Disease Diagnostic Testing Algorithm in Special Instructions for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions.

Reference Values:
Negative: <20.0 U
Weak positive: 20.0-30.0 U
Positive: >30.0 U
Reference values apply to all ages.

Clinical References:

DGGL 89030

Gliadin (Deamidated) Antibody, IgG, Serum

Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process that occurs in genetically susceptible individuals following ingestion of wheat, rye, or barley proteins.(1) The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy.(1) Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and/or constipation.(2) Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis.(3) Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma.(1,2) The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency.(1,3) Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population.(3) A definitive
diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy. (1-3) Given the invasive nature and cost of the biopsy, serologic tests may be used to identify individuals with a high probability of having celiac disease. Because no single laboratory test can be relied upon completely to establish a diagnosis of celiac disease, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures. Celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies. (4) Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. (2) The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. Testing for IgA and IgG antibodies to unmodified gliadin proteins is no longer recommended because of the low sensitivity and specificity of these tests for celiac disease; however, recent studies have identified specific B-cell epitopes on the gliadin molecule that, when deamidated by the enzyme tissue transglutaminase, have increased sensitivity and specificity for celiac disease. (5,6) The tests for deamidated gliadin antibodies, IgA and IgG, replace the older gliadin antibody tests, which have been discontinued at Mayo Clinic. The sensitivity and specificity of test DGLDN / Gliadin (Deamidated) Antibodies Evaluation, IgG and IgA, Serum for untreated, biopsy-proven celiac disease were comparable to TSTGP / Tissue Transglutaminase (tTG) Antibodies, IgA and IgG Profile, Serum in a recent study conducted at Mayo Clinic. (5) The treatment for celiac disease is maintenance of a gluten-free diet. (1-3) In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves. This is typically accompanied by an improvement in clinical symptoms. For evaluation purposes, all serologic tests ordered for the diagnosis of celiac disease should be performed while the patient is on a gluten-containing diet. Once a patient has initiated the gluten-free diet, serologic testing may be repeated to assess the response to treatment. In some patients, it may take up to 1 year for antibody titers to normalize. Persistently elevated results suggest poor adherence to the gluten-free diet or the possibility of refractory celiac disease. (1) See Celiac Disease Diagnostic Testing Algorithm in Special Instructions for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions. For your convenience, we recommend utilizing cascade testing for celiac disease. Cascade testing ensures that testing proceeds in an algorithmic fashion. The following cascades are available; select the appropriate one for your specific patient situation. Algorithms for the cascade tests are available in Special Instructions. -CDCOM / Celiac Disease Comprehensive Cascade: complete testing including HLA DQ -CDSP / Celiac Disease Serology Cascade: complete testing excluding HLA DQ -CDGF / Celiac Disease Gluten-Free Cascade: for patients already adhering to a gluten-free diet To order individual tests, see Celiac Disease Diagnostic Testing Algorithm in Special Instructions.

**Useful For:** Evaluating patients suspected of having celiac disease; this includes patients with symptoms compatible with celiac disease, patients with atypical symptoms, and individuals at increased risk of celiac disease Evaluating the response to treatment with a gluten-free diet

**Interpretation:** Positive test results for deamidated gliadin antibodies, IgA or IgG, are consistent with the diagnosis of celiac disease. Negative results indicate a decreased likelihood of celiac disease. Decreased levels of deamidated gliadin antibodies, IgA or IgG, following treatment with a gluten-free diet are consistent with adherence to the diet. Persistence of high levels of antibodies following dietary treatment suggest poor adherence to the diet or the presence of refractory disease.

**Reference Values:**
Negative: <20.0 U
Weak positive: 20.0-30.0 U
Positive: >30.0 U
Reference values apply to all ages.

**Clinical References:**
Glial Fibrillary Acidic Protein (GFAP) Immunostain, Technical Component Only

Clinical Information: Glial fibrillary acidic protein (GFAP) is an intermediate filament protein of 52 kD found in glial cells, astrocytes, and ependymal cells. Immunoperoxidase staining for GFAP produces intense cytoplasmic staining of astrocytes, glial cells, and ependymal cells in normal brain. In neoplastic tissues, GFAP is useful for the identification of glial tumors such as astrocytomas and ependymomas.

Useful For: Classification of glial tumors

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

Glipizide (Glucotrol)

Reference Values:
Units: ng/mL

Plasma insulin concentrations have been shown to increase only when plasma glipizide concentrations exceeded 200 ng/mL.

Toxic range has not been established.

Globotriaosylsphingosine, Serum

Clinical Information: Fabry disease is an X-linked recessive lysosomal storage disorder caused by a deficiency of the enzyme alpha-galactosidase A (alpha-Gal A). Reduced enzyme activity results in accumulation of glycosphingolipids in the lysosomes throughout the body, in particular, the kidney, heart, and brain. Severity and onset of symptoms are dependent on the residual enzyme activity. Symptoms may include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, corneal opacity, renal insufficiency leading to end-stage renal disease, and cardiac and cerebrovascular disease. There are renal and cardiac variant forms of Fabry disease that may be underdiagnosed. Heterozygous females of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected, and they may have alpha-Gal A activity in the normal range. The estimated incidence varies from 1 in 3,000 infants detected via newborn screening to 1 in 10,000 males.
diagnosed after onset of symptoms. Unless irreversible damage has already occurred, treatment with enzyme replacement therapy (ERT) has led to significant clinical improvement in affected individuals. For this reason, early diagnosis and treatment are desirable, and in a few US states early detection of Fabry disease through newborn screening has been implemented. Absent or reduced alpha-Gal A in blood spots, leukocytes (AGA / Alpha-Galactosidase, Leukocytes), or serum (AGAS / Alpha-Galactosidase, Serum) can indicate a diagnosis of classic or variant Fabry disease. Molecular sequence analysis of the GLA gene (FABRZ / Fabry Disease, Full Gene Analysis) allows for detection of the disease-causing mutation in males and females. Molecular genetic testing is the recommended diagnostic test for females as alpha-galactosidase activity may be in the normal range in an affected female patient. The glycosphingolipid, globotriaosylsphingosine (LGb3), may be elevated in symptomatic patients and supports a diagnosis of Fabry disease. It may also be helpful as a tool for monitoring disease progression as well as determining treatment response in known patients. In addition, measurement or globotriaosylsphingosine (LGb3), may provide additional diagnostic information in the evaluation of uncertain cases, such as in asymptomatic heterozygous females, individuals with novel GLA variants of unclear clinical significance, as well as asymptomatic patients identified by family screening.

**Useful For:** Diagnosis and monitoring of Fabry disease

**Interpretation:** Elevation of globotriaosylsphingosine (Lyso-GB3) is diagnostic for Fabry disease.

**Reference Values:**

< or =1.0 ng/mL

**Clinical References:**


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**Glomerular Basement Membrane Antibodies, IgG, Serum**

**Clinical Information:** Antibodies to glomerular basement membrane (GBM) antigens cause glomerulonephritis, Goodpasture syndrome (glomerulonephritis, often with rapid onset renal failure, and pulmonary hemorrhage), and, less commonly, pulmonary hemosiderosis.(1) Nephrogenic GBM antigens are associated with the noncollagenous carboxyl extension of type IV procollagen. The immunologic stimuli that elicit production of GBM antibodies are not known. There is some evidence of a genetic association with HLA-DR2. GBM antibody-mediated glomerulonephritis and Goodpasture syndrome occur with a bimodal age distribution primarily in males ages 20 to 40 and in patients older than age 50. Glomerulonephritis without pulmonary involvement is more common in the older age group, and shows a female predominance.

**Useful For:** Evaluating patients with rapid onset renal failure or pulmonary hemorrhage, as an aid in the diagnosis of Goodpasture syndrome

**Interpretation:** Positive results are consistent with Goodpasture syndrome. Glomerular basement membrane antibodies detected by immunoassay have been reported to be highly specific for Goodpasture syndrome. The sensitivity of this test approaches 87% in untreated patients with systemic disease.(1)

**Reference Values:**

<1.0 U (negative)

> or =1.0 U (positive)

Reference values apply to all ages.

**Clinical References:** 1. Pusey CD: Anti-glomerular basement membrane disease. Kidney Int
**Glucagon (GLUC) Immunostain, Technical Component Only**

**Clinical Information:** Glucagon is a polypeptide hormone produced by the (a) cells of the pancreatic islets in response to hypoglycemia or to stimulation by growth hormone. Cytoplasmic staining is seen in pancreatic islet glucagon (a) cells and islet cell tumors. Glucagon is also found in neuroendocrine cells of the small intestine and stomach.

**Useful For:** Aids in the study of islet-cell tumors and some endocrine tumors of the gastrointestinal tract

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Reference Values:**
N/A

**Clinical References:**

**Glucagon, Plasma**

**Clinical Information:** Glucagon is a single-chain polypeptide of 29 amino acids that is derived from a larger precursor peptide (big plasma glucagon), which is cleaved upon secretion. The main sites of glucagon production are the hypothalamus and pancreatic alpha-islet cells. The function of hypothalamic glucagon is incompletely understood and currently no clinical disorders of hypothalamic glucagon function have been defined. Pancreatic islet glucagon is secreted in response to hypoglycemia, with resultant increases in blood glucose concentration. Glucagon's hyperglycemic effect is produced by stimulating hepatic glycogenolysis and gluconeogenesis; it has no effect on muscle glycogen. Once blood-glucose levels have normalized, glucagon secretion ceases. Excessive glucagon secretion can lead to hyperglycemia or aggravate preexisting hyperglycemia. Excessive and inappropriate glucagon secretion can sometimes be observed in diabetes, in particular during ketoacidosis, and can complicate management of the disorder. In rare cases, it also can occur in tumors of the pancreatic islets (glucagonoma); carcinoid tumors and other neuroendocrine neoplasms and hepatocellular carcinomas. Patients with glucagon-secreting tumors may present with classic glucagonoma syndrome, consisting of necrotic migratory erythema, diabetes, and diarrhea, but also can have more subtle symptoms and signs. Decreased or absent glucagon response to hypoglycemia can be seen in type I diabetes (insulin-dependent diabetes) and can contribute to severe and prolonged hypoglycemic responses.

**Useful For:** Diagnosis and follow-up of glucagonomas and other glucagon-producing tumors Assessing diabetic patients with problematic hyper- or hypoglycemic episodes (extremely limited utility) Glucagon is routinely measured along with serum glucose, insulin, and C-peptide levels, during the mixed-meal test employed in the diagnostic workup of suspected postprandial hypoglycemia.
However, it plays only a minor role in the interpretation of this test.

**Interpretation:** Elevated glucagon levels in the absence of hypoglycemia may indicate the presence of a glucagon-secreting tumor. Successful treatment of a glucagon-secreting tumor is associated with normalization of glucagon levels. Inappropriate elevations in glucagon levels in hyperglycemic type I diabetic patients indicate that paradoxical glucagon release may contribute to disease severity. This can be observed if insulin treatment is inadequate and patients are ketogenic. However, glucagon measurement plays little, if any, role in the diagnostic workup of diabetic ketoacidosis, which is based on demonstrating significantly elevated plasma or serum glucose (>250 mg/dL), circulating ketones (beta-hydroxy butyrate), and acidosis (typically with increased anion gap). In diabetic patients, low glucagon levels (undetectable or in the lower quartile of the normal range) in the presence of hypoglycemia indicate impairment of hypoglycemic counter-regulation. These patients may be particularly prone to recurrent hypoglycemia. This can be a permanent problem due to islet alpha-cell destruction or other, less well understood processes (e.g., autonomous neuropathy). It can also be functional, most often due to over tight blood-glucose control, and may be reversible after decreasing insulin doses.

**Reference Values:**

- < or =6 hours: 100-650 pg/mL
- 1-2 days: 70-450 pg/mL
- 2-4 days: 100-650 pg/mL
- 4-14 days: declining gradually to adult levels
- >14 days: < or =80 pg/mL (range based on 95% confidence limits)

Glucagon levels are inversely related to blood glucose levels at all ages. This is particularly pronounced at birth and shortly thereafter, until regular feeding patterns are established. This explains the higher levels immediately after birth, which then first fall as the glucagon release mobilizes the infant's glucose stores, then rise again as stores are depleted, finally normalizing towards adult levels as regular feeding patterns are established.

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.

**Clinical References:**

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**Glucopsycho sine, Blood Spot**

**Clinical Information:** Gaucher disease is an autosomal recessive lysosomal storage disorder caused by a deficiency of the enzyme, beta-glucosidase. Beta-glucosidase facilitates the lysosomal degradation of glucosylceramide (glucocerebroside) and glucopsycho sine (glucosylsphingosine). Gaucher disease is caused by mutations in the GBA gene. There are 3 described types of Gaucher disease with varying clinical presentations and age of onset from a perinatal lethal disorder to an asymptomatic type. Features of all types of Gaucher disease include hepatosplenomegaly and hematological abnormalities. Gaucher disease type I is the most common, representing more than 90% of cases. It is generally characterized by bone disease, hepatosplenomegaly, anemia and thrombocytopenia, coagulation abnormalities, lung disease, but no central nervous system (CNS) involvement. Gaucher disease types II and III are characterized by the presence of primary neurologic disease. In addition, Type II typically presents with limited psychomotor development, hepatosplenomegaly, and lung disease, resulting in death usually between 2 and 4 years of age. Individuals with Gaucher disease type III may present prior to 2 years of age, but the progression is not as rapid and patients may survive into the third and fourth decade. Further subtypes of Gaucher disease include a perinatal lethal form associated with skin abnormalities and
nonimmune hydrops fetalis, and a cardiovascular form presenting with calcification of the aortic and mitral valves, mild splenomegaly, corneal opacities, and gaze impairment. Treatment is available in the form of enzyme replacement therapy and/or substrate reduction therapy for types I and III. These treatment options have generally made bone marrow transplantation obsolete. Currently, only supportive therapy is available for type II because of the inability of enzyme provided by replacement therapy to cross the blood-brain barrier. The incidence of Gaucher disease type I ranges from 1 in 30,000 to 1 in 100,000 in the general population, but is much more frequent among Ashkenazi Jews with an incidence of approximately 1 in 900. Types II and III both have an incidence of approximately 1 in 100,000 in the general population. A diagnostic workup for Gaucher disease may demonstrate the characteristic finding of Gaucher cells on bone marrow examination, other hematologic abnormalities, and hepatosplenomegaly. The diagnosis can be confirmed by the demonstration of reduced or absent acid beta-glucosidase activity in leukocytes (BGL / Beta-Glucosidase, Leukocytes) and molecular genetic analysis of the GBA gene (GAUP / Gaucher Disease, Mutation Analysis, GBA; or GBAZ / Gaucher Disease, Full Gene Analysis). Glucosylsphingosine is elevated in symptomatic patients and supports a diagnosis of Gaucher disease. It may also be helpful in determining treatment response.

**Useful For:** Quantification of glucosylsphingosine (glucosylsphingosine) in dried blood spots supports the biochemical diagnosis of Gaucher disease may aid in monitoring a patientâ€™s response to treatment

**Interpretation:** An elevation of glucosylsphingosine is indicative of Gaucher disease.

**Reference Values:**
Normal <47 nmol/L glucosylsphingosine

**Clinical References:**

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**Glucose Phosphate Isomerase, Erythrocytes**

**Clinical Information:** Erythrocyte glucose phosphate isomerase (GPI) deficiency has been reported as a cause of chronic hemolysis in numerous cases. Inheritance is autosomal recessive. Hemolytic disease of the newborn is a common presenting manifestation of GPI deficiency.

**Useful For:** A second-order test in the evaluation of individuals with chronic hemolysis

**Interpretation:** Glucose phosphate isomerase (GPI) deficiency causes a moderately severe anemia. GPI values can be 25% of normal. Increased GPI activity may be seen when young red blood cells are being produced in response to the anemia (reticulocytosis) or in the case of a newborn.

**Reference Values:**
> or =12 months: 39.3-57.7 U/g Hb
Reference values have not been established for patients who are <12 months of age.

**Glucose, 24 Hour, Urine**

**Clinical Information:** Under normal circumstances, glucose is readily filtered by glomeruli and the filtered glucose is reabsorbed by the proximal tubule; essentially no glucose is normally excreted in the urine. However, the capacity for the proximal tubule to reabsorb glucose is limited; if the filtered load exceeds the proximal tubule's reabsorptive capacity, a portion of the filtered glucose will be excreted in the urine. Thus, elevated serum glucose concentrations (such as occur with diabetes mellitus) may result in an increase in filtered load of glucose and may overwhelm the tubules' reabsorptive capacity resulting in glucosuria. Additionally, conditions which adversely affect proximal tubule function may also result in decreased reabsorption of glucose, and increased urinary glucose concentration, even in the presence of normal plasma glucose concentrations. Some of these conditions include Fanconi syndrome, Wilson's disease, hereditary glucosuria, and interstitial nephritis. These conditions are relatively rare, and most causes for elevated urine glucose concentrations are due to elevated serum glucose levels.

**Useful For:** Limited usefulness in the screening or management of diabetes mellitus

**Interpretation:** Elevated urine glucose concentration reflects either the presence of hyperglycemia or a defect in proximal tubule function. As a screening test for diabetes mellitus, urine glucose testing has a low sensitivity (though reasonably good specificity).

**Reference Values:**
< or =0.15 g/24 hours


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**Glucose, Body Fluid**

**Clinical Information:** Glucose: Blood glucose is measured to assess the glycemic state of a patient. Body fluid glucose concentrations that are lower than expected indicate increased cellularity and, therefore, glycolysis within the body fluid space and serves as an indicator of infection or possibly malignancy. Body fluid glucose concentrations are expected to be lower than that found in serum or plasma. Ideally they are measured in the fasting state whereby glucose is able to equilibrate into the space the body fluid is contained within. Pleural fluid: Low pleural fluid glucose concentrations (<40-60 mg/dL) indicate a complicated parapneumonic or malignant effusion. However, low glucose is not specific for infection or malignancy and may be attributed to hemothorax, tuberculosis, rheumatoid, or lupus pleuritis, among other diseases. pH is the preferred test for making this determination when available. Pericardial fluid: Pericardial fluid glucose has been investigated on a limited basis. In presumed normal specimens collected during surgery, pericardial fluid-to-serum ratio for glucose was 1.0 (95% CI, 0.8-1.2). Peritoneal fluid: Ascitic fluid glucose should be interpreted in conjunction with serum glucose measurement. In a cohort of noninfected patients with alcohol-related cirrhosis, the mean (SD) ascitic fluid-to-serum glucose ratio was 1.04 (0.25). Ascitic fluid glucose may be helpful in differentiating spontaneous bacterial peritonitis from secondary peritonitis caused by bowel perforation. Secondary peritonitis is likely if 2 of the 3 following criteria are met: 1) total protein >1 g/dL; 2) LDH >225 IU/L (or greater than the upper limit of normal for serum); and 3) glucose <50 mg/dL. Amniotic fluid: Amniotic fluid is produced by the amnion and placenta, representing a plasma ultrafiltrate. Amniocentesis may be performed to assess fetal distress. Intraamniotic infection or chorioamnionitis is an acute inflammation of the fetal membranes commonly caused by bacterial infection prompting an inflammatory response leading to labor and term or preterm birth. Chorioamnionitis may be symptomatic (clinical) or asymptomatic (histological) occurring most often during prolonged labor or as a consequence of membrane rupture as bacteria have greater opportunity to ascend the lower genital tract to colonize the uterus. Prompt diagnosis and treatment for clinical chorioamnionitis is critical to avoid maternal and fetal morbidity and mortality. Culture and gram stain are often used in the assessment of infection, however, gram stain lacks sensitivity and culture results are not returned in a timely enough manner to make clinical decisions. Low glucose concentrations have been associated with positive culture results and consequently poor outcomes. Synovial fluid: Synovial fluid is present in joint cavities and serves a number of important roles in
maintaining joint health and mobility. Symptoms of joint problems include pain, swelling, stiffness, or decreased range of motion. Routine analysis of synovial fluid includes Gram stain, culture, crystal analysis, and cell count with WBC differential. In normal synovial fluid, glucose concentrations are similar to those observed in fasting serum. Low synovial fluid glucose has been associated with septic arthritis or inflammation.(7)

**Useful For:** Aiding in the diagnosis of infection

**Interpretation:** Pleural fluid: Glucose <60 mg/dL is typically associated with low fluid pH. Pericardial and peritoneal fluids: Fluid to serum glucose ratio <1.0 may be useful in differentiating infective from parainfective effusions. Amniotic fluid: Glucose <16 mg/dL is associated with positive culture results. Synovial fluid: Glucose concentrations are typically within 10 mg/dL of fasting plasma glucose concentrations or approximately one-half of the nonfasting plasma glucose concentration.

**Reference Values:**
Not applicable

**Clinical References:**
7. Margaretten ME, Kohlwes J, Moore D, Bent S: Does this adult patient have septic arthritis? JAMA 2007;297:1478-1488

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**Glucose, Random, Serum**

**Clinical Information:** The most common disease related to carbohydrate metabolism is diabetes mellitus, which is characterized by insufficient blood levels of active insulin. Symptoms include polyuria, abnormally elevated blood and urine glucose values, excessive thirst, constant hunger, sudden weight loss, and possibly elevated blood and urine ketones. Complications from diabetes are the third leading cause of death in the United States. There are approximately 16 million diabetics in the United States, and that number is growing. It is estimated that at least 5 million of these people have not been diagnosed. The prevalence in the population age 65 and older is 18.4%, representing 6.3 million cases. The cost of diabetes to the US economy exceeds $92 billion annually. Overproduction or excess administration of insulin causes a decrease in blood glucose to levels below normal. In severe cases, the resulting extreme hypoglycemia is followed by muscular spasm and loss of consciousness, known as insulin shock.

**Useful For:** Diagnosing and managing diabetes mellitus and other carbohydrate metabolism disorders including gestational diabetes, neonatal hypoglycemia, idiopathic hypoglycemia, and pancreatic islet cell carcinoma

**Interpretation:** Any of the following results, confirmed on a subsequent day, can be considered diagnostic for diabetes: -Fasting plasma or serum glucose > or =126 mg/dL after an 8-hour fast -2-Hour plasma or serum glucose > or =200 mg/dL during a 75-gram oral glucose tolerance test (OGTT) -Random glucose >200 mg/dL, plus typical symptoms Patients with "impaired" glucose regulation are those whose fasting serum or plasma glucose fall between 101 and 126 mg/dL, or whose 2-hour value on oral glucose tolerance test fall between 140 and 199 mg/dL. These patients have a markedly increased risk of developing type 2 diabetes and should be counseled for lifestyle changes and followed up with more testing. Indications for screening and testing include strong family history, marked obesity, history of babies over 9 pounds, and recurrent skin and genitourinary infections. Glucose levels of 25 mg/dL or lower in infants younger than 1 week are considered to be potentially life threatening, as
are glucose levels of 40 mg/dL or lower in infants older than 1 week. Glucose levels of 400 mg/dL and higher are considered a critical value.

**Reference Values:**
0-11 months: not established
> or =1 year: 70-140 mg/dL


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**Glucose, Random, Urine**

**Clinical Information:** Under normal circumstances, glucose is readily filtered by glomeruli and the filtered glucose is reabsorbed by the proximal tubule; essentially no glucose is normally excreted in the urine. However, the capacity for the proximal tubule to reabsorb glucose is limited; if the filtered load exceeds the proximal tubule's reabsorptive capacity, a portion of the filtered glucose will be excreted in the urine. Thus, elevated serum glucose concentrations (as seen with diabetes mellitus) may result in an increase in filtered load of glucose and may overwhelm the tubules' reabsorptive capacity resulting in glucosuria. Glucosuria occurs when the renal threshold for glucose is exceeded (typically >180 mg/dL). This is most commonly, although not exclusively, seen in diabetes. Additionally, conditions which adversely affect proximal tubule function may also result in decreased reabsorption of glucose, and increased urinary glucose concentration, even in the presence of normal plasma glucose concentrations. Some of these conditions include Fanconi syndrome, Wilson disease, hereditary glucosuria, and interstitial nephritis. These conditions are relatively rare, and most causes for elevated urine glucose concentrations are due to elevated serum glucose levels.

**Useful For:** An indicator of abnormal proximal tubule function Limited usefulness in the screening or management of diabetes mellitus

**Interpretation:** Elevated urine glucose concentration reflects either the presence of hyperglycemia or a defect in proximal tubule function. As a screening test for diabetes mellitus, urine glucose testing has a low sensitivity (though reasonably good specificity).

**Reference Values:**
< or =15 mg/dL


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**Glucose, Spinal Fluid**

**Clinical Information:** Cerebrospinal fluid (CSF) is secreted by the choroid plexuses, around the cerebral vessels, and along the walls of the ventricles of the brain, filling the ventricles and cisternae and bathing the spinal cord. CSF is reabsorbed into the blood through the arachnoid villi. CSF turnover is rapid, exchanging about 4 times per day. CSF glucose levels may be decreased due to consumption by microorganisms, impaired glucose transport, or increased glycolysis. Elevated CSF glucose levels are consistent with hyperglycemia.

**Useful For:** Investigating possible central nervous system infection

**Interpretation:** Cerebrospinal fluid (CSF) glucose levels may be decreased in any central nervous system infection, although levels are typically normal in viral meningitis, low in bacterial meningitis, and may be normal or low in fungal meningitis. CSF glucose levels are normally about 60% of blood glucose levels.

**Reference Values:**
Spinal fluid glucose concentration should be approximately 60% of the plasma/serum concentration and should be compared with concurrently measured plasma/serum glucose for adequate clinical
Glucose-6-Phosphate Dehydrogenase (G-6-PD), Quantitative, Erythrocytes

Clinical Information: Hemolytic disease may be associated with deficiency of erythrocyte enzymes. The most commonly encountered is a deficiency of glucose-6-phosphate dehydrogenase (G6PD). The G6PD locus is on the X chromosome and, thus, G6PD deficiency is a sex-linked disorder. Affected males (hemizygotes) inherit the abnormal gene from their mothers who are almost always asymptomatic carriers (heterozygotes). More than 300 molecular variants of G6PD are known, and the clinical and laboratory features of G6PD deficiency vary accordingly. With some variants, there is chronic, life-long hemolysis, but much more commonly, the condition is asymptomatic and only results in susceptibility to acute hemolytic episodes, which may be triggered by some medications, ingestion of fava beans, viral, or bacterial infections. It is also associated with neonatal hyperbilirubinemia. The major G6PD variants occur in specific ethnic groups. Thus, knowledge of the ethnic background of the patient is important. G6PD deficiency has very high frequency in Southeast Asians and is the most common cause of hemolytic disease of the newborn in Southeast Asian neonates. It is also seen in persons of African and Mediterranean descent. Rasburicase therapy is contraindicated in patients with G6PD deficiency. Deficiency can be assessed by enzymatic and/or genetic assays. If deficient status can be unambiguously assigned by genotyping, that is sufficient. However, due to the limitations of genetic testing, in most cases it is necessary to perform G6PD enzyme testing to assign G6PD status (adapted from Relling et al).(1)

Useful For: Evaluation of individuals with Coombs-negative nonspherocytic hemolytic anemia
Rapid testing to assess glucose-6-phosphate dehydrogenase (G6PD) enzyme capacity prior to Rasburicase therapy

Interpretation: Abnormal values are usually 0% to 20% of normal mean. Intermediate values can occur in some genetic variants and in female carriers.

Reference Values:
> or =12 months: 8.8-13.4 U/g Hb

Reference values have not been established for patients who are <12 months of age.

hydrogen peroxide and other sources of oxidative stress. G6PD is encoded by the gene G6PD, which lies on the X-chromosome. G6PD deficiency is inherited in an X-linked recessive manner; therefore, males are more commonly affected than females, but due to the high prevalence of G6PD deficiency, homozygous and compound heterozygous females are not uncommon. A large number of G6PD pathogenic variants have been discovered. These variants are subdivided into a class system based on definitions from the World Health Organization (WHO). Table 1. G6PD variant WHO class and associated G6PD deficiency phenotype WHO class Associated Clinical Presentation G6PD activity I Chronic nonspherocytic hemolytic anemia (CNSHA) <10% II Asymptomatic unless challenged <10% III Asymptomatic unless challenged 10%-60% IV None Normal With the exception of those with chronic nonspherocytic hemolytic anemia (CNSHA), individuals with G6PD deficiency are typically asymptomatic until they are challenged with an exogenous factor such as a drug, infection, or fava beans. The exogenous factor can trigger acute hemolytic anemia (AHA) in individuals with G6PD deficiency. The severity of AHA is highly variable, ranging from mild to life-threatening and can be fatal. Therefore, determining the G6PD deficiency status is recommended on the FDA label of several drugs either proven or suspected to cause AHA in patients with G6PD deficiency. For a list of drugs known to cause AHA in individuals with G6PD deficiency, see Pharmacogenomic Associations Table in Special Instructions. Preemptive genotyping allows for the identification of patients at risk for an adverse reaction to drugs known to cause AHA in those with G6PD deficiency. In most cases, genotyping provides sufficient information to avoid the use of contraindicated drugs. In some cases, including heterozygous females, the phenotyping assay is necessary to determine if such drugs should be avoided. Skewed X-inactivation in heterozygous females has been reported to result in G6PD deficiency, but the phenotyping assay is necessary to determine G6PD activity level. For more information regarding the need for G6PD enzyme activity follow-up testing to this genotyping assay, refer to the G6PD Genotyping Algorithm for Therapeutic Drug Recommendations in Special Instructions.

Useful For: Genetic test for individuals at high risk for G6PD deficiency (for initial or time-sensitive screening for G6PD deficiency, refer to phenotyping enzyme assay G6PD / Glucose-6-Phosphate Dehydrogenase [G-6-PD], Quantitative, Erythrocytes) Aiding in the diagnosis of glucose-6-phosphate dehydrogenase (G6PD) deficiency Determining G6PD deficiency status in individuals with inconclusive or unexpected phenotyping results Differentiation of heterozygous females with skewed X-inactivation from homozygous and compound heterozygous females Definitive diagnosis of carrier status in females Evaluation of neonates (particularly males) with unexplained jaundice Identifying individuals at risk of drug-induced acute hemolytic anemia (AHA) related to G6PD deficiency

Interpretation: All detected alterations will be evaluated according to the latest American College of Medical Genetics recommendations.(1) Variants will be classified based on known, predicted, or possible effect on gene pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


**HEX4**

**Glucotetrasaccharides, Urine**

Clinical Information: Pompe disease, also known as glycogen storage disease type II, is an
autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA). This leads to an accumulation of glycogen in the lysosome causing swelling, cell damage, and progressive organ dysfunction. In glycogen storage diseases, excess glycogen is degraded to glucose tetrasaccharide (Glc4), which is excreted in urine. Measurement of Glc4 in urine is used for both initial diagnosis and monitoring of patients with Pompe disease. Pompe disease is caused by mutations in the GAA gene. The classic, early infantile onset variant of the disease is characterized by progressive muscle hypotonia, weakness, hypertrophic cardiomyopathy, and death due to either cardiorespiratory or respiratory failure typically by the end of the first year of life. Juvenile and adult-onset variants of Pompe disease are characterized by later onset and longer survival. Primary symptoms of later-onset Pompe disease include muscle weakness and respiratory insufficiency, with cardiomyopathy only rarely developing. Based on data from newborn screening, the incidence is approximately 1 in 20,000 live births with most patients being affected with later onset variants of Pompe disease. The clinical phenotype depends on residual enzyme activity, with complete loss of activity causing onset in infancy. Enzyme replacement therapy (ERT) improves outcome in many patients with either classic infantile onset or later onset forms of Pompe disease. Early initiation of treatment improves the prognosis and makes early diagnosis of Pompe disease desirable. Because of this, newborn screening for Pompe disease has recently been added to the Recommended Uniform Screening Panel and already been implemented in some states. Historically, diagnostic testing required a skin or muscle biopsy to measure GAA enzyme activity. Today, noninvasive enzyme assays and molecular genetic analysis of the GAA gene (GAAZ / Pompe Disease, Full Gene Analysis) are available for testing in blood and dried blood spots. In addition, Glc4 can be measured in urine to support a diagnosis of Pompe disease and other glycogen storage disorders.

**Useful For:** In conjunction with acid alpha-glucosidase enzyme activity assays and molecular genetic analysis of the GAA gene Monitoring Pompe patients on enzyme replacement therapy May also support the diagnosis and monitoring of other glycogen storage disorders; however, glucose tetrasaccharide (Glc4) excretion appears to be less consistently elevated in glycogen storage disorders other than Pompe disease

**Interpretation:** An elevated excretion of glucotetrasaccharide is indicative of Pompe disease or other glycogen storage disorders.

**Reference Values:**
- < or =14 months: < or =14.9 mmol/mol Cr
- > or =15 months: < or =4.0 mmol/mol Cr

**Clinical References:**

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**GLUT-1 Immunostain, Technical Component Only**

**Clinical Information:** GLUT-1 is a ubiquitous facilitative membrane glucose transporter that is activated by hypoxia-sensing cellular pathways and may sustain cellular metabolism via glycolysis when hypoxia is present. It is expressed at high levels on red blood cells, the endothelium of the blood brain barrier, and the perineurium. Various carcinomas may show overexpression, including fallopian tube carcinomas.

**Useful For:** Identification of erythrocytes in various normal and neoplastic tissues

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the...
context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Reference Values:**

N/A


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**Glutamic Acid Decarboxylase (GAD65) Antibody Assay, Serum**

**Clinical Information:** Glutamic acid decarboxylase (GAD) is a neuronal enzyme involved in the synthesis of the neurotransmitter gamma-aminobutyric acid (GABA). Antibodies directed against the 65-kd isoform of GAD (GAD65) are seen in a variety of autoimmune neurologic disorders including stiff-man (Moersch-Woltman) syndrome, autoimmune cerebellitis, brain stem encephalitis, seizure disorders, neuromyelitis optica and other myelopathies, myasthenia gravis, Lambert-Eaton syndrome, and dysautonomia. GAD65 antibody is also the major pancreatic islet antibody and an important serological marker of predisposition to type 1 diabetes. GAD65 autoantibody also serves as a marker of predisposition to other autoimmune disease that occur with type 1 diabetes, including thyroid disease (eg, thyrotoxicosis, Grave disease, Hashimoto thyroiditis, hypothyroidism), pernicious anemia, premature ovarian failure, Addison disease, (idiopathic adenocortical failure) and vitiligo.

**Useful For:** Assessing susceptibility to autoimmune (type 1, insulin-dependent) diabetes mellitus and related endocrine disorders (eg, thyroiditis and pernicious anemia). Titors generally < or =0.02 nmol/L. A second islet cell antibody (IA-2) is more predictive for development of type 1 diabetes, but less frequent than glutamic acid decarboxylase (GAD65) antibody amongst diabetic patients. Insulin autoantibodies also serve as a marker of susceptibility to type 1 diabetes. Distinguishing between patients with type 1 and type 2 diabetes. Assays for IA-2, insulin, gastric parietal cell, thyroglobulin, and thyroid peroxidase antibodies, complement GAD65 antibody in this context; titers generally < or =0.02 nmol/L. Confirming a diagnosis of stiff-man syndrome, autoimmune encephalitis, cerebellitis, brain stem encephalitis, myelitis; titers generally > or =0.03 nmol/L. Confirming susceptibility to organ-specific neurological disorders (eg, myasthenia gravis, Lambert-Eaton syndrome); titers generally < or =0.02 nmol/L

**Interpretation:** High titers (> or =0.02 nmol/L) are found in classic stiff-man syndrome (93% positive) and in related autoimmune neurologic disorders (eg, acquired cerebellar ataxia, some acquired nonparaneoplastic encephalomyelopathies). Diabetic patients with polyendocrine disorders also generally have glutamic acid decarboxylase (GAD65) antibody values > or =0.02 nmol/L. Values in patients who have type 1 diabetes without a polyendocrine or autoimmune neurologic syndrome are usually < or =0.02 nmol/L. Low titers (0.03-19.9 nmol/L) are detectable in the serum of approximately 80% of type 1 diabetic patients. Conversely, low titers are detectable in the serum of <5% of type 2 diabetic patients. Low titers are found in approximately 25% of patients with myasthenia gravis, Lambert-Eaton syndrome, and rarer autoimmune neurological disorders. Eight percent of healthy Olmsted County residents over age 50 have low-positive values. These are not false positive; the antibodies are inhibited by unlabeled GAD65 antigen and are accompanied in at least 50% of cases by related organ-specific autoantibodies. Values > or =0.03 nmol/L are consistent with susceptibility to autoimmune (type 1) diabetes and related endocrine disorders (thyroiditis and pernicious anemia).
Glutamic Acid Decarboxylase (GAD65) Antibody Assay, Spinal Fluid

**Clinical Information:** Glutamic acid decarboxylase (GAD) is a neuronal enzyme involved in the synthesis of the neurotransmitter gamma-aminobutyric acid (GABA). Serum antibodies directed against the 65-kd isoform of GAD (GAD65) are detected in heightened frequency in a variety of autoimmune neurologic disorders, including stiff-man (Moersch-Woltman) syndrome, autoimmune cerebellitis, some idiopathically acquired epilepsies, some rare acquired encephalomyelopathies with and without neoplasia, and in myasthenia gravis and Lambert-Eaton myasthenic syndrome. GAD65 antibodies account for the majority of clinically recognized pancreatic islet cell antibodies, and are an important serological marker of predisposition to type 1 (insulin-dependent) diabetes. GAD65 autoantibodies also serve as a marker of predisposition to autoimmune disorders that commonly or sometimes coexist with type 1 diabetes, including autoimmune thyroid disease (eg, thyrotoxicosis, Graves disease, Hashimoto thyroiditis, hypothyroidism), pernicious anemia, premature ovarian failure, Addison disease (idiopathic adrenocortical failure), and vitiligo. GAD65 antibodies are found in the serum of approximately 8% of healthy subjects older than age 50, usually in low titer, but often accompanied by related "thyrogastric" autoantibodies.

**Useful For:** Possible use in evaluating patients with stiff-man syndrome, autoimmune cerebellitis and other acquired central nervous system disorders affecting gabaminergic neurotransmission

**Interpretation:** Intrathecal synthesis of GAD65 antibody has been demonstrated in patients with stiff-man syndrome, but cerebrospinal fluid (CSF) values are log orders lower than serum. We have not determined the frequency of GAD65 antibodies in CSF of patients with various diagnoses.

**Reference Values:**
< or =0.02 nmol/L

**Clinical References:**

Glutamine Synthetase (GS) Immunostain, Technical Component Only

**Clinical Information:** Glutamine synthetase (GS) is an enzyme that catalyzes the ATP-dependent condensation of glutamate with ammonia to form glutamine. GS can be used with a panel of immunohistochemistry markers (beta-catenin, liver fatty acid binding protein, C-reactive protein, and
amyloid A) to distinguish hepatic adenoma from focal nodular hyperplasia and nonneoplastic liver. GS, a target gene of beta-catenin, is expressed in hepatic adenomas with beta-catenin mutations (type 2), but is not expressed in hepatic adenomas without beta-catenin mutations. GS is expressed in zone 3 of normal liver and has a characteristic map-like pattern in focal nodular hyperplasia.

**Useful For:** Classification of hepatic adenomas and the identification of focal nodular hyperplasia

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Reference Values:**
N/A

**Clinical References:**

**Gluten IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation* 2.0 Upper Limit of Quantitation** 200

**Reference Values:**
< 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Gluten, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease.
and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to
identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm
sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of
allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with
the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
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</tr>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Clinical References:** Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and
Management by Laboratory Methods. 21st edition. Edited by RA McPherson, MR Pincus. WB

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**Glycerol-Corrected Triglycerides, Serum**

**Clinical Information:** Triglycerides are esters of glycerol with 3 long-chain fatty acids. Increased
plasma triglyceride concentrations are indicative of a metabolic abnormality and, along with elevated
cholesterol, are considered a risk factor for atherosclerotic disease. Hyperlipidemia may be inherited or
associated with biliary obstruction, diabetes mellitus, nephrotic syndrome, renal failure, or metabolic
disorders related to endocrinopathies. Increased triglycerides may also be medication-induced (e.g.,
prednisone). See Lipids and Lipoproteins in Blood Plasma in Special Instructions. Traditional,
nonglycerol-blanked methods for measuring triglycerides break down plasma and serum triglycerides
into glycerol and fatty acids. The glycerol is then measured in an enzymatic colorimetric assay.
Consequently, patients with elevated free glycerol in circulation will have a falsely elevated triglyceride
concentration, pseudohypertriglyceridemia, when using a nonglycerol-blanked triglyceride assay.
Glycerol is an intermediate in the conversion of glucose to lipids and serves as the precursor for
triglyceride and other glycerolipids. Patients with type 2 diabetes mellitus, hyperthyroidism, those who
are obese, or those receiving oral or parenteral supplementation with glycerol may have slightly higher
free glycerol in circulation, however this increase is unlikely to affect triglyceride result interpretation.
Glycerol kinase deficiency (GKD) is an X-linked genetic condition leading to impaired function of
glycerol kinase (GK), the primary regulator of glycerol entry into metabolic pathways. Insufficient GK
activity leads to extreme elevations in plasma glycerol concentrations (i.e., hyperglycerolemia) and
glyceroluria. Patients with GKD may be placed on a glycerol-restricted diet and instructed to avoid
prolonged periods of fasting. GKD is divided into 3 clinical forms: -Complex GKD involves mutations
in the GK locus and 2 others (adrenal hypoplasia congenital: AHC and Duchenne muscular dystrophy: DMD) on Xp21 and manifests in infants. -Juvenile GKD is associated with metabolic and central
nervous system instability and deterioration. Juvenile GKD usually presents in the early years of life as
repeated vomiting, acidemia, and central nervous system depression. - Adult GKD is mainly benign
with detection usually found incidentally by pseudohypertriglyceridemia.

**Useful For:** Evaluation of pseudohypertriglyceridemia for possible glycerol kinase deficiency
Evaluation of triglyceride as a cardiovascular risk factor in individuals with elevated cholesterol values

**Interpretation:** Patients with glycerol kinase deficiency typically have serum free glycerol concentrations greater than 10 fold above normal.

**Reference Values:**

**TRIGLYCERIDE, TOTAL and CORRECTED**

The National Cholesterol Education Program (NCEP) has set the following guidelines in adults ages 18 and up:

- Normal: <150 mg/dL
- Borderline high: 150-199 mg/dL
- High: 200-499 mg/dL
- Very high: > or =500 mg/dL

The National Cholesterol Education Program (NCEP) and National Health and Nutrition Examination Survey (NHANES) has set the following guidelines in children ages <2:

- <2 years: Reference values have not been established for patients who are <24 months of age.

- 2-9 years:
  - Acceptable: <75 mg/dL
  - Borderline high: 75-99 mg/dL
  - High: > or =100 mg/dL

- 10-17 years:
  - Normal: <90 mg/dL
  - Borderline high: 90-129 mg/dL
  - High: > or =130 mg/dL

**GLYCEROL, CALCULATED**

- <18 years: Reference values have not been established for patients who are <18 years of age.
- >18 years: 40-370 mc mol/L

**Clinical References:**

additional information. Gene Disease Name OMIM ID Inheritance AGL Glycogen storage disease type III 232400 AR ALDOA Glycogen storage disease XII 611881 AR ENO3 Glycogen storage disease XIII 612932 AR EPMA2 Lafora progressive myoclonus epilepsy 254780 AR G6PC Glycogen storage disease type Ia, mitochondrial 232200 AR GAA Pompe disease-glycogen storage disease type II 232300 AR GBE1 Glycogen storage disease type IV-adult polyglucosan body disease 232500, 263570 AR GY1 Glycogen storage disease type XV 613507 AR GYS1 Glycogen storage disease type 0-muscle 611556 AR GYS2 Glycogen synthase 2 (glycogen storage disease 0, liver) 240600 AR LAMP2 Glycogen storage disease type IIb-Danon disease 300257 XLD LDHA Glycogen storage disease type XI- lactate dehydrogenase deficiency 612933 AR NHLRC1 Lafora progressive myoclonus epilepsy 254780 AR PFKM Glycogen storage disease type VII 232800 AR PGAM2 Glycogen storage disease type X-phosphoglycerate mutase deficiency 261670 AR PKG1 Phosphoglycerate kinase deficiency 300653 XLR PMG1 Phosphoglyceromutase 1 (glycogen storage disease XIV) 614921 AR PHKA1 Phosphorylase kinase, alpha 1 (muscle) (Glycogen storage disease, type IXD) 300559 XLR PHKA2 Glycogen storage disease type IXA 306000 XLR PHKB Glycogen storage disease, IXb 261750 AR PHKG2 Glycogen storage disease type IXC 613027 AR PRKAG2 Glycogen storage disease of the heart -Wolff-Parkinson-White syndrome 194200, 261740 AD PYGL Glycogen storage disease type VI 232700 AR PYGM Glycogen storage disease type V, McArdle disease 232600 AR SLC2A2 Glycogen storage disease type 11, GLUT-2 deficiency, Fanconi Bickel syndrome 2227810 AR SLC37A4 Glycogen storage disease type Ib and Ic 232220 AR AR=autosomal recessive AD=autosomal dominant XLD=X-linked recessive

Useful For: Follow up of abnormal biochemical results consistent with glycogen storage disease
Identifying mutations within genes known to be associated with glycogen storage disease, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values:
An interpretive report will be provided.


GlycoMark

Reference Values:

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<th>Age</th>
<th>Range</th>
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<td>&lt;18 y</td>
<td>Not Established</td>
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<tr>
<td>Adult Males</td>
<td>10.7 â€“ 32.0</td>
</tr>
<tr>
<td>Adult Females</td>
<td>6.8 â€“ 29.3</td>
</tr>
</tbody>
</table>

GlycoMark is intended for use with managing glycemic control in diabetic patients. A low result corresponds to high glucose peaks.

1. 5-AG blood levels can be affected by clinical conditions or medications.
**Glycophorin A (CD235a) Immunostain, Technical Component Only**

**Clinical Information:** Glycophorin A is expressed by erythroid precursors in the bone marrow, and is also present on red blood cells.

**Useful For:** Aids in the identification of erythroid precursors in bone marrow

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Reference Values:**

N/A

**Clinical References:**

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**Glycyphagus domesticus, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Class IgE kU/L  Interpretation

0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive

Reference values apply to all ages.


GLYP3

Glypican-3 Immunostain, Technical Component Only

Clinical Information: Glypican-3 (GPC3) protein is a member of the glypican family of heparin sulfate proteoglycans that are phosphatidylinositol-anchored to the cytoplasmic membrane. GPC3 acts as a coreceptor for heparin-binding growth factors, which play an important role in cell growth and differentiation. Diagnostically, GPC3 will aid in separating hepatocellular carcinomas from other malignancies and hepatic adenomas. It is expressed in 70% to 90% of hepatocellular carcinomas.

Useful For: Aids in differentiating hepatocellular carcinomas from other malignancies and hepatic adenomas

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Reference Values: N/A


GNPTZ

GNPTAB Gene, Full Gene Analysis

Clinical Information: N-acetylglucosamine-1-phosphate transferase, alpha and beta subunits (GNPTAB)-related mucolipidoses are progressive lysosomal storage diseases traditionally classified as...
mucolipidosis II and mucolipidosis III based upon their severity and disease onset. These conditions have substantial clinical overlap and mutation testing can aid the diagnosis. Mucolipidosis II alpha/beta (ML II alpha/beta or I-cell disease) is a progressive inborn error of metabolism with clinical onset at birth and fatal outcome most often in early childhood. Postnatal growth is limited and often ceases in the second year of life; contractures develop in all large joints. The skin is thickened, facial features are coarse, and gingiva are hypertrophic. Orthopedic abnormalities present at birth may include thoracic deformity, kyphosis, clubfeet, deformed long bones, and hip dislocation. There is often cardiac involvement, most commonly thickening and insufficiency of the mitral valve and, less frequently, the aortic valve. Progressive mucosal thickening narrows the airways and gradual stiffening of the thoracic cage contributes to respiratory insufficiency, the most common cause of death. Mucolipidosis III alpha/beta (ML III alpha/beta or pseudo-Hurler polydystrophy) is a slowly progressive disorder with clinical onset at approximately 3 years of age. It is characterized by a slow growth rate and subnormal stature; radiographic evidence of mild-to-moderate dysostosis multiplex; joint stiffness and pain initially in the shoulders, hips, and fingers; gradual mild coarsening of facial features; and normal to mildly impaired cognitive development. If present, organomegaly is mild. Pain from osteoporosis that is clinically and radiologically apparent in childhood becomes more severe from adolescence.

Cardiorespiratory complications (restrictive lung disease, thickening and insufficiency of the mitral and aortic valves, left and/or right ventricular hypertrophy) are common causes of death, typically in early to middle adulthood. ML II/ML III alpha/beta are inherited in an autosomal recessive manner. Both disorders have been reported from nearly all parts of the world and the overall carrier rate ranges between 1 in 158 and 1 in 316. GNPTAB is the gene in which mutations are most often known to cause ML II/ML III alpha/beta. Bidirectional sequencing of the entire GNPTAB coding region detects 2 disease-causing mutations in more than 95% of individuals with ML II/ML III alpha/beta. This gene encodes 2 of 3 subunits (alpha/beta) of the heterohexameric enzyme, N-acetylglucosamine-1-phosphotransferase. In the absence of this enzyme, a mannone 6-phosphate (M6P) recognition marker is not added to lysosomal hydrolases and other glycoproteins. This leads to disruption of acid hydrolases transport to the lysosome. Formation of the M6P recognition marker on lysosomal hydrolases is significantly reduced in ML III alpha/beta, and nearly or totally absent in ML II alpha/beta. To confirm or establish the diagnosis in a proband requires a combination of clinical evaluation and laboratory testing. The use of the following diagnostic testing is recommended:

Identification of characteristic clinical and radiographic findings, assay of oligosaccharides in urine, assay of several acid hydrolases in plasma, sequence analysis of GNPTAB. The activity of nearly all lysosomal hydrolases in plasma and other body fluids is higher in individuals affected with ML II alpha/beta (5- to 20-fold) and ML III alpha/beta (up to 10-fold) than in normal controls. ML II/ML III alpha/beta is diagnosed by assay of N-acetylglucosamine-1-phosphotransferase in skin fibroblasts. Demonstration of nearly complete inactivity (<1%) of the enzyme confirms the diagnosis of ML II alpha/beta, whereas significant deficiency (1%-10% of normal) of this enzyme is suggestive of the diagnosis of ML III alpha/beta. Urinary excretion of oligosaccharides is often excessive. Prior to molecular analysis, the delineation of ML II alpha/beta from ML III alpha/beta depended solely on clinical criteria including age of onset, rate of progression, and overall severity. Molecular genetic studies reveal a genotype-phenotype correlation supporting the clinical distinction between ML II alpha/beta and ML III alpha/beta. Mutations that completely inactivate the phosphotransferase consistently result in ML II alpha/beta, irrespective of their location within the gene. Mutations with less adverse effect on this enzyme activity usually result in ML III alpha/beta or occasionally in intermediate phenotypes. (1, 2)

**Useful For:** Molecular diagnosis or carrier status of mucolipidosis II alpha/beta and mucolipidosis III alpha/beta in conjunction with identification of characteristic clinical, radiographic, and biochemical findings, and genetic counseling for family members

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
**Goat Epithelium, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>6</td>
<td>&gt; 100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


**Goat's Milk, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and...
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>Strongly positive Reference values apply to all ages.</td>
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Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


FGNRH
90165
Gonadotropin Releasing Hormone (Gn-RH)
Clinical Information: Gonadotropin-Releasing Hormone (Gn-RH), also known as Luteinizing Hormone-Releasing Hormone (LH-RH), is a Decapeptide secreted pulsatily from the hypothalamus. It stimulates the release of the Gonadotropins - Luteinizing Hormone and Follicle Stimulating Hormone - exerting a stronger effect on Luteinizing Hormone. Testosterone and Estradiol, whose release is stimulated by the Gonadotropins, exert a negative feedback control on LH-RH both at the hypothalamic site and by decreasing pituitary receptor binding. LH-RH levels are low in patients with hypothalamic hypogonadism differentiating them from the high levels usually found in primary hypopituitary hypogonadism. Accentuation of the LH-RH pulse occurs at the onset of puberty triggering the release of LH and FSH required in pubertal development. LH-RH is stimulated by Epinephrine and suppressed by Dopamine and opiates. LH-RH and some of its agonists are frequently used to induce ovulation.

Reference Values:
Adult Reference Range(s):
Males: 4.0 - 8.0 pg/mL
Females: 2.0 - 10.0 pg/mL

GOOS
82714
Goose Feathers, IgE
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm
sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Gram Stain**

**Clinical Information:** The Gram stain is a general stain used extensively in microbiology for the preliminary differentiation of microbiological organisms. The Gram stain is one of the simplest, least expensive, and most useful of the rapid methods used to identify and classify bacteria. The Gram stain is used to provide preliminary information concerning the type of organisms present directly from clinical specimens or from growth on culture plates. This stain is used to identify the presence of microorganisms in normally sterile body fluids (cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid). It is also used to screen sputum specimens to establish acceptability for bacterial culture (<25 squamous epithelial cells per field is considered an acceptable specimen for culture) and may reveal the causative organism in bacterial pneumonia.

**Useful For:** Identifying microorganisms in normally sterile body fluids Screening sputum specimens for acceptability for bacterial culture Guiding initial antimicrobial therapy

**Interpretation:** During the staining process, the crystal violet and iodine form a complex within the heat fixed cell. In gram-negative organisms, this complex is readily washed out by the acetone-alcohol. They appear red because they retain only the safranin dye (counterstain). Gram-positive organisms retain the crystal violet-iodine complex after decolorization and remain purple. Cells and Organisms will be reported according to the following tables: White Blood Cells Epithelial Cells Organisms Low Power Field (LPF-10x) Rare (R) $<$ or $=1$ Oil Immersion Field (OIF-100x) Rare (R) $<$1 Few (F) 1-9 Few (F) 1-5 Moderate (O) 10-25 Moderate (O) 6-30 Many (M) $>$25 Many (M) $>$30

**Reference Values:** No organisms seen or descriptive report of observations.

Gram Stain for Bacterial Vaginosis

**Clinical Information:** Bacterial vaginosis is so-named because bacteria are the cause and an associated inflammatory response is lacking. It results in an increase in thin, gray, homogeneous vaginal discharge and vaginal malodor and is caused by a change in the vaginal flora. Bacterial vaginosis is a synergistic polymicrobial infection not caused by a specific organism. The standard scoring system termed the "Nugent score" is a technique for assessing bacterial vaginosis using microscopic examination of a Gram-stained smear of vaginal discharge.

**Useful For:** Supporting the diagnosis of bacterial vaginosis

**Interpretation:** Assessment of a Gram-stained slide using the Nugent score has replaced culture as the preferred test to diagnose bacterial vaginosis.(1) While Gardnerella is the most common anaerobe found in bacterial vaginosis, other anaerobic organisms are often present along with a decrease in the amount of "usual flora" (eg, Lactobacillus species). This system uses a 0- to 4-point scale to calculate the weighted sum of the following 3 bacterial morphotypes: Lactobacillus, Gardnerella/Bacteroides, and Mobiluncus species. A total score of greater than 6 is considered abnormal, a total score of 4 to 6 is considered a transitional stage, and a total score of 0 to 3 is considered normal. Clue cells and yeast are also reported, if present.

**Reference Values:**
One of the 3 following reports dependent on the weighted sum balance of Lactobacillus, Gardnerella/Bacteroides, and Mobiluncus species:
1. Consistent with normal bacterial vaginal flora.
2. Altered vaginal flora not consistent with bacterial vaginosis. This frequently represents a transitional stage. If signs or symptoms persist, repeat testing is warranted.
3. Consistent with bacterial vaginosis.

**Clinical References:** CAP Microbiology checklist: Bacterial Vaginosis-Evaluation of a criterion-based Gram stain is used for the microscopic diagnosis of bacterial vaginosis. 2011

Gram-Negative Bacillus Antimicrobial Resistance Genes, PCR Panel

**Clinical Information:** The Check-MDR CT103XL panel, which is performed on bacterial isolates, detects 27 genes associated with antimicrobial resistance in Gram-negative bacilli. Antibiotic resistance is evolving as a result of use and overuse of antibacterial agents. Characterizing the molecular mechanisms of antimicrobial resistance can be helpful to explain unusual phenotypic susceptibility profiles or for epidemiologic purposes. A myriad of beta-lactamase enzymes may be found in Gram-negative bacteria; these enzymes hydrolyze (break down) the beta-lactam ring of beta-lactam antibiotics, destroying their antibacterial activity. A single bacterial isolate may carry 1 or more genes that code for the production of a beta-lactamase enzyme. Beta-lactamases can be on the chromosome or on plasmids and may be classified as extended-spectrum beta-lactamases (ESBLs), AmpCs, and carbapenemases, among other types. ESBLs are beta-lactamases with an expanded substrate profile and are typically plasmid-borne. They are capable of hydrolyzing first-, second-, third- and fourth-generation cephalosporins, penicillins, and monobactams. TEM, SHV, and CTX-M genes are the most clinically prevalent. -TEM and SHV subtypes are derived from the parental sequences by point mutations resulting in amino acid substitutions, which allow the enzymes to hydrolyze a wide range of beta-lactam antibiotics. -CTX-M genes originate from Kluyvera species and can be separated into 5 different groups based on their amino acid sequence: CTX-M-1, CTX-M-2, CTX-M-9, CTX-M-8, and CTX-M-25. -VEB, PER, BEL, and GES genes are less common. AmpC cephalosporinases hydrolyze almost all beta-lactam antibiotics including penicillins, cephalosporins, and monobactams and may be chromosomally- or plasmid-encoded. Several Enterobacteriaceae carry a chromosomal copy of an AmpC gene. AmpC Gene Origin of Chromosomal Gene CMY II Citrobacter freundii DHA Morganella morganii FOX Aeromonas caviae ACC Hafnia alvei ACT/MIR Enterobacter cloacae and Enterobacter asburiae CMY I/MOX Aeromonas hydrophilia -Plasmid-encoded AmpC genes may be shared among bacteria. Plasmid-encoded AmpC genes may produce a higher amount of beta-lactamase as compared to chromosomally-encoded AmpC genes; knowing the mechanism may be useful in assessing treatment.

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
An AmpC gene detected in a species that does not have a chromosomal AmpC (see table above) suggests that the gene is plasmid-encoded. Carbapenemases show general resistance to all beta-lactam antibiotics including the beta-lactam-beta-lactamase inhibitor combinations and elevated or complete resistance against carbapenem antibiotics. In addition, isolates harboring carbapenemases often have additional beta-lactamase genes and genes for resistance to quinolones and aminoglycosides. -Klebsiella pneumoniae Carbapenemase (KPC) is a plasmid-encoded carbapenemase first identified in Klebsiella pneumoniae isolates in North America. KPC has since spread to many parts of the world and can be found in several species of the Enterobacteriaceae. -New Delhi Metallo-beta-lactamase (NDM) was first reported in 2009 from a patient of Indian origin in Sweden. It is prevalent in the Indian subcontinent, but has spread worldwide. -The oxacillinase group consists of 10 members, of which OXA-48 and OXA-181 are the most prevalent variants. OXA-48 occurs predominantly in Enterobacteriaceae, originated from Shewanella species, and is most prevalent in Europe and the North African subcontinent. Another grouping of OXA-type carbapenemases are found in Acinetobacter species and consists of 3 type members, OXA-23, OXA-24, and OXA-58. Each type has several subtypes. -VIM, a metallo-beta-lactamase, was first found in 1997 in a Pseudomonas aeruginosa isolate in Verona. It may be found in Enterobacteriaceae and includes at least 38 variants of which the DNA sequences may differ significantly. -IMP, a metallo-beta-lactamase, was detected in Japan in 1990 (IMP-1) in Pseudomonas aeruginosa. It may be found worldwide in Enterobacteriaceae and includes at least 44 members with varying gene sequences. -GIM-1 and SPM-1, also metallo-beta-lactamases, are less frequently found carbapenemases. GIM-1 originated in Germany and has been found in Pseudomonas aeruginosa, Enterobacteriaceae, and Acinetobacter spp. SPM-1 producing Pseudomonas aeruginosa is endemic in Brazilian hospitals where it has been associated with numerous outbreaks. -GES gene family consists of both ESBL-types and carbapenemase types. Content was based on the Check-MDR CT103XL User Manual and reproduced with permission by Wouter de Levita of Check-Points, 2016.

Useful For: Characterizing the molecular mechanisms of antimicrobial resistance in Gram-negative bacilli to explain unusual phenotypic susceptibility profiles or for epidemiologic purposes. The panel detects the following beta-lactamase enzyme producing genes: Carbapenemase Genes: GES (Carbapenemase) GIM IMP KPC NDM OXA-23 like OXA-24 like OXA-48 like OXA-58 like SPM VIM ESBL Genes: BEL CTX-M1 Group CTX-M2 Group CTX-M9 Group CTX-M8/25 Group GES (ESBL) PER SHV TEM VEB AmpC Genes: ACC ACT/MIR CMY MOX CMYII DHA FOX

Interpretation: A negative or positive result is reported for each gene type assayed. A positive result confirms the presence of a particular beta-lactamase gene in the bacterial isolate tested.

Reference Values: Not applicable


Granulocyte Antibodies, Serum

Clinical Information: Granulocyte antibodies are induced by pregnancy or prior transfusion and are associated with febrile, nonhemolytic transfusion reactions. Patients who have been immunized by previous transfusions, pregnancies, or allografts frequently experience febrile, nonhemolytic transfusion reactions which must be distinguished from hemolysis before further transfusions can be safely administered. Granulocyte antibodies may also be present in autoimmune neutropenia.

Useful For: The work-up of individuals having febrile, nonhemolytic transfusion reactions The detection of individuals with autoimmune neutropenia

Interpretation: A positive result in an individual being worked up for a febrile transfusion reaction
indicates the need for leukocyte-poor (filtered) red blood cells. This test cannot distinguish between allo-
and autoantibodies

Reference Values:
Not applicable

Clinical References: Verheugt FW, von dem Borne AE, Decary F, Engelfreit CP: The detection of

GRANB
Granzyme B (GRAN B) Immunostain, Technical Component Only

Clinical Information: Granzyme B is a cytotoxic granule-associated protein, expressed
constitutively in natural killer cells and in activated cytotoxic T cells. The immunostain is used to
characterize T-cell lymphomas with a cytotoxic phenotype.

Useful For: Classification of lymphomas

Interpretation: This test includes only technical performance of the stain (no pathologist
interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the
context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology
Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with
the case is required. Additional specific stains may be requested as part of the pathology consultation,
and will be performed as necessary at the discretion of the Mayo pathologist. The positive and
negative controls are verified as showing appropriate immunoreactivity and documentation is retained at
Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant
quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test
should be performed in the context of the patient's clinical history and other diagnostic tests by a
qualified pathologist.

Reference Values:
N/A

Clinical References:
2. Morice WG, Kurtin PJ, Tefferi A, Hanson CA: Distinct bone marrow findings in T-cell granular
lymphocytic leukemia revealed by paraffin section immunoperoxidase stains for CD8, TIA1, and
granzyme B. Blood 2002;99(1):268-274

FGRPG
Grape IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:
<2 mcg/mL.

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical
utility of food-specific IgG tests has not been established. These tests can be used in special clinical
situations to select foods for evaluation by diet elimination and challenge in patients who have
food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be
taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in
question. This test should only be ordered by physicians who recognize the limitations of the test.

GRAP
Grape, IgE
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


Grapefruit, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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**Grass Panel # 1**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Grass Panel # 3**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**GAB1**

**GRB2-Associated Binding Protein 1 (GAB1) Immunostain, Technical Component Only**

**Clinical Information:** GAB1 (growth factor receptor bound protein 2-associated protein 1) is an adapter protein that is involved in growth, transformation, and apoptosis. GAB1 can be used with a panel of immunohistochemical markers in the classification of medulloblastomas into SHH (sonic hedgehog), WNT (wingless-type murine mammary tumor), or non-SHH/WNT subgroups.

**Useful For:** Identification and differentiation of medulloblastomas
**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**Greek Fennel, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
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<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
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<tr>
<td>6</td>
<td>&gt; or =100</td>
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Reference values apply to all ages.

**Green Coffee Bean, IgE**

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Green Pea, IgE**

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Green Pepper, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
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**Green String Bean, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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ALDR
82671 Grey Alder, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
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6 > or =100 Strongly positive Reference values apply to all ages.


GRHPZ
35444 GRHPR Gene, Full Gene Analysis
Primary hyperoxaluria type 2 (PH2) is a hereditary disorder of glyoxylate metabolism caused by deficiency of the hepatic enzyme glyoxylate reductase/hydroxypyruvate reductase (GRHPR). Absence of GRHPR activity results in excess oxalate and usually L-glycerate excreted in the urine leading to nephrolithiasis (kidney stones) and sometimes renal failure. Onset of PH2 is typically in childhood or adolescence with symptoms related to kidney stones. In some cases, kidney failure may be the initial presenting feature. Nephrocalcinosis, as seen by renal ultrasound, is observed less frequently in individuals with PH2 than primary hyperoxaluria type 1 (PH1). End-stage renal disease (ESRD) is also less common and of later onset than PH1; however, once ESRD develops, oxalate deposition in other organs such as bone, retina, and myocardium can occur. While the exact prevalence and incidence of PH2 are not known, it is thought that PH2 is less common than PH1, which has an estimated prevalence rate of 1 to 3 per million population and an incidence of 0.1 per million/year. Biochemical testing is indicated in patients with possible primary hyperoxaluria. Measurement of urinary oxalate in a timed, 24-hour urine collection is strongly preferred, with correction to adult body surface area in pediatric patients (HYOX / Hyperoxaluria Panel, Urine; OXU / Oxalate, Urine). In very young children (incapable of performing a timed collection), random urine oxalate to creatinine ratios may be used for determination of oxalate excretion. In patients with reduced kidney function, POXA / Oxalate, Plasma is also recommended. Urinary excretion of oxalate of >1.0 mmol/1.73 m(2)/24 hours is strongly suggestive of, but not diagnostic, for primary hyperoxaluria as there are other forms of inherited hyperoxaluria (PH1 and non-PH1/PH2) and secondary hyperoxaluria that may result in similarly elevated urine oxalate excretion rates. An elevated urine glyceral in the presence of hyperoxaluria is suggestive of PH2. Caution is warranted in interpretation of urine oxalate excretion in patients with reduced kidney function as urine oxalate concentrations may be lower due to reduced glomerular filtration rate. Historically, the diagnosis of PH2 was confirmed by GRHPR enzyme analysis performed on liver biopsy; however, this has been replaced by molecular testing, which forms the basis of confirmatory or carrier testing in most cases. PH2 is inherited as an autosomal recessive disorder caused by mutations in the GRHPR gene, which encodes the enzyme GRHPR. Two common GRHPR mutations have been identified: c.103delG and c.403_404+2delAAGT. These mutations account for about one-third of the mutant alleles described in the Northern European Caucasian population and about 15% in the Asian population. Direct sequencing of the GRHPR gene will identify these 2 mutations as well as other common or novel mutations associated with PH2.

Confirming a diagnosis of primary hyperoxaluria type 2 (PH2) Carrier testing for individuals with a family history of PH2 in the absence of known mutations in the family

All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity, and reported with interpretive comments detailing their potential or known significance.

An interpretive report will be provided.


Streptococcus pyogenes (group A streptococcus) is a common cause of pharyngitis and skin and soft tissue infection. In children, S pyogenes can cause perianal infection. The classic presentation is a well-demaricated rash around the anus with itching, rectal pain, and
occasionally, blood-streaked stools. Untreated, painful defecation, toilet avoidance, and constipation may persist for months, until effective treatment is administered. Anal fissures may ensue. A swab of the affected area may be submitted for S. pyogenes culture to confirm the diagnosis. Health care workers may transmit S. pyogenes to their patients (eg, in the postsurgical setting) leading to outbreaks of invasive disease. Screening of health care workers or other patients for S. pyogenes may be requested by Infection Prevention and Control as part of an investigation of a potential nosocomial case (or cases). Isolates may be typed to assess strain relatedness.

**Useful For:** Diagnosis of perianal cellulitis
Screening patients and health care workers for Streptococcus pyogenes for the purpose of investigating possible nosocomial transmission

**Interpretation:** Positive cultures are reported out as Streptococcus pyogenes.

**Reference Values:**
Negative

**Clinical References:**

**CGBS 87346**

**Group B Streptococcus (Streptococcus agalactiae) Culture**

**Clinical Information:** Streptococcus agalactiae (group B streptococcus) is a cause of morbidity and mortality among infants. Infections occurring within the first week of life are considered early-onset; those occurring in infants >1 week of age are considered late-onset. Maternal vaginal or rectal colonization with Streptococcus agalactiae is a risk factor for early-onset disease in infants. Ten to 30% of pregnant women are vaginally or rectally colonized with Streptococcus agalactiae and may transmit the organism to their infant during labor and delivery. The Centers for Disease Control and Prevention recommends screening for colonization with Streptococcus agalactiae at 35 to 37 weeks gestation as a guide for intrapartum antibiotic prophylaxis to decrease the risk of infection with Streptococcus agalactiae in the infant.

**Useful For:** Screening for maternal colonization with Streptococcus agalactiae at 35 to 37 weeks gestation as a guide for intrapartum antibiotic prophylaxis to decrease the risk of infection by Streptococcus agalactiae in the infant

**Interpretation:** Positive cultures are reported out as Streptococcus agalactiae.

**Reference Values:**
Negative

**Clinical References:**

**FGRPR 57943**

**Grouper IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal/Borderline 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 High Positive 4 17.50 â€“ 49.99 Very High Positive 5 50.00 â€“ 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**
<0.35 kU/L
Growth Differentiation Factor 15 (GDF15), Plasma

**Clinical Information:** Mitochondria perform many important metabolic functions, the most vital being the production of energy in the form of adenosine triphosphate (ATP) through the electron-transport chain and the oxidative phosphorylation system, which consists of 5 complexes (complex I-V). Each of these complexes consists of 4 to 46 subunits encoded by both nuclear and mitochondrial DNA. Mitochondrial diseases are caused by defects in any of the relevant metabolic pathways and have an estimated prevalence of 1:8,500. Mitochondrial diseases are varied, including mitochondrial DNA deletion syndromes such as Kearns-Sayre syndrome (KSS), mitochondrial depletion syndromes such as those caused by mutations in the TK2 and SUCLA2 or POLG and C10orf2 genes, and mitochondrial point mutation syndromes such as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), as well as others. The clinical features of mitochondrial diseases vary widely, but they can include lactic acidosis, myopathy, ophthalmoplegia, ptosis, cardiomyopathy, sensorineural hearing loss, optic atrophy, pigmented retinopathy, diabetes mellitus, encephalomyopathy, seizures, and stroke-like episodes. A diagnostic workup for a mitochondrial disorder may demonstrate elevations of the lactate-to-pyruvate ratio (LAA / Lactate, Plasma and PYR / Pyruvic Acid, Blood) and an elevated growth differentiation factor 15 (GDF15) level. GDF15 is a protein of the transforming growth factor beta superfamily. GDF15 is overexpressed in muscle and serum in patients with various types of mitochondrial diseases, including those with mitochondrial deletion, depletion, and point mutation syndromes. Therefore, increased levels of GDF15 can indicate the need for further investigations including molecular studies and muscle biopsy to confirm the presence of a possible neuromuscular mitochondrial disease.

**Useful For:** A circulating biomarker in myopathy-related mitochondrial disease as well as other conditions Investigation of patients suspected of having a mitochondrial myopathy

**Interpretation:** Abnormal results along with clinical findings may be suggestive of mitochondrial disease. Additional workup is indicated.

**Reference Values:**
- 3 months* and older: ≤ 750 pg/mL
  - *This test is not recommended for infants <3 months of age due to the high levels of GDF15 contributed from the placenta during pregnancy.

**Clinical References:**

Growth Hormone (GH) Immunostain, Technical Component Only

**Clinical Information:** Growth hormone (GH) is a 21-kD polypeptide hormone that stimulates protein synthesis and may act primarily via the somatomedins. Somatroph cells produce GH and constitute a high proportion of anterior pituitary cells (50%). GH shows cytoplasmic staining of normal pituitary somatotroph cells and GH adenomas. Globular juxtanuclear staining may be present in some adenomas.

**Useful For:** Aids in the identification of growth hormone adenomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with
the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**Growth Hormone, Serum**

**Clinical Information**: The anterior pituitary secretes human growth hormone (hGH) in response to exercise, deep sleep, hypoglycemia, and protein ingestion. hGH stimulates hepatic insulin-like growth factor-1 and mobilizes fatty acids from fat deposits to the liver. Hyposecretion of hGH causes dwarfism in children. Hypersecretion causes gigantism in children or acromegaly in adults. Because hGH levels in normal and diseased populations overlap, hGH suppression and stimulation tests are needed to evaluate conditions of hGH excess and deficiency; random hGH levels are inadequate.

**Useful For**: Diagnosis of acromegaly and assessment of treatment efficacy (in conjunction with glucose suppression test) Diagnosis of human growth hormone deficiency (in conjunction with growth hormone stimulation test)

**Interpretation**: Acromegaly: For suppression testing, normal subjects have a nadir growth hormone (GH) concentration of <0.3 ng/mL after ingestion of a 75-gram glucose dose. Patients with acromegaly fail to show normal suppression. Using the Access ultrasensitive hGH assay, a cutoff of 0.53 ng/mL for nadir GH was found to most accurately differentiate patients with acromegaly in remission from active disease with a sensitivity of 97% (95% CI, 83%-100%) and a specificity of 100% (95% CI, 82%-100%).(1) Deficiency: A normal response following stimulation tests is a peak GH concentration >5 ng/mL in children and >4 ng/mL in adults. For children, some experts consider GH values between 5 ng/mL and 8 ng/mL equivocal and only GH peak values >8 ng/mL as truly normal. Low levels, particularly under stimulation, indicate human growth hormone deficiency.

**Reference Values**:

**Adults**
- Males: 0.01-0.97 ng/mL
- Females: 0.01-3.61 ng/mL

Reference intervals have not been formally verified in-house for pediatric and adolescent patients. The published literature indicates that reference intervals for adult, pediatric, and adolescent patients are comparable.

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.

FIRGH 90161

**Growth Hormone-Releasing Hormone (GH-RH)**

**Clinical Information:** Growth Hormone Releasing Hormone is a 44 amino acid peptide produced primarily by the hypothalamus. It is a neurohumoral control for adenohypophyseal secretion of Growth Hormone. Other hypothalamic hormones have a stimulatory effect on pituitary hormones, but Growth Hormone Releasing Hormone has no known effect on other pituitary hormones. Somatostatin is the inhibitory counterpart of Growth Hormone Releasing Hormone. Growth Hormone Releasing Hormone has structural similarities with the Secretin-Glucagon family of gastrointestinal hormones. Growth Hormone Releasing Hormone has been isolated from pancreatic islet cells and various cancer tumor cells.

**Reference Values:**
Levels of IR-GH-RH
Baseline ranges: 5 - 18 pg/mL

GGUM 82479

**Guar Gum, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L Interpretation
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Guava, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Guinea Pig Epithelium, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from

Current as of October 11, 2018 2:20 pm CDT   800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Reference values apply to all ages.


**Gum Arabic, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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**Reference Values:**
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


**FCGUM 57969**
**Gum Carageenan IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**<0.35 kU/L

**FGUMX 57974**
**Gum Xanthan IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**<0.35 kU/L

**FHACK 57951**
**Hackberry (Celtis occidentalis) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal/Borderline 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 High Positive 4 17.50 â€“ 49.99 Very High Positive 5 50.00 â€“ 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**<0.35 kU/L
Haddock (Melanogrammus aeglefinus) IgE

**Interpretation:**
- Class IgE (kU/L)
- Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.4 Moderate Positive 3 3.5 â€“ 17.4 High Positive 4 17.5 â€“ 49.9 Very High Positive 5 50.0 â€“ 99.9 Very High Positive 6 >100 Very High Positive

**Reference Values:**
<0.35 kU/L

Haemophilus influenzae Type B Antibody, IgG, Serum

**Clinical Information:**
Haemophilus influenzae type B (HIB) is an encapsulated gram-negative cocco-bacillary bacterium that can cause devastating disease in young children including meningitis, bacteremia, cellulitis, epiglottitis, pneumonia, and septic arthritis. One of the great advances in modern medicine has been the development of an effective vaccine against HIB. A patient's immunological response to HIB vaccine can be determined by measuring anti-HIB IgG antibody using this EIA technique.

**Useful For:**
- Assessing a patient's immunological (IgG) response to Haemophilus influenzae type B (HIB) vaccine
- Assessing immunity against HIB
- Aiding in the evaluation of immunodeficiency

**Interpretation:**
- An anti-Haemophilus influenzae type B (HIB) IgG antibody concentration of 0.15 mg/L is generally accepted as the minimum level for protection at a given time; however, it does not confer long-term protection. A study from Finland suggested that the optimum protective level is 1.0 mg/L postimmunization.(1) Furthermore, studies have shown that the response to HIB vaccine is age-related. By testing pre- and postvaccination patient serum specimens, this test may be used to aid diagnosis of immunodeficiency.

**Reference Values:**
> or =0.15 mg/L
- Reference values apply to all ages.

**Clinical References:**

Hairy Cell Leukemia (DBA44) Immunostain, Technical Component Only

**Clinical Information:**
Hairy cell leukemia (DBA.44) antibody recognizes an unknown, fixation-resistant antigen that is expressed in normal mantle zone B-cells. It may be expressed in endothelial cells, monocytoid B cells, and scattered immunoblasts as well. It is characteristically expressed in hairy cell leukemia, as well as a subset of marginal zone lymphomas, and may be useful in classification of these lymphomas.

**Useful For:**
Classification of lymphomas

**Interpretation:**
This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a...

Hake, Fish, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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**Halibut IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**Halibut, IgE**

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**Haloperidol, Serum**

**Clinical Information:** Haloperidol (Haldol) is a member of the butyrophenone class of neuroleptic drugs used to treat psychotic disorders (eg. schizophrenia). It is also used to control the tics and verbal utterances associated with Tourette's syndrome and in the management of intensely hyperexcitable children who fail to respond to other treatment modalities. The daily recommended oral dose for patients with moderate symptoms is 0.5 to 2.0 mg; for patients with severe symptoms, 3 to 5 mg may be used. However, some patients will respond only at significantly higher doses. Haloperidol is metabolized in the liver to reduced haloperidol, its major metabolite.(1,2) Use of haloperidol is associated with significant toxic side effects, the most serious of which include tardive dyskinesia which can be irreversible, extrapyramidal reactions with Parkinson-like symptoms, and neuroleptic malignant syndrome. Less serious side effects can include hypotension, anticholinergic effects (blurred vision, dry mouth, constipation, urinary retention), and sedation. The risk of developing serious, irreversible side effects seems to increase with increasing cumulative doses over time.(1,3)

**Useful For:** Optimizing dosage Monitoring compliance Assessing toxicity

**Interpretation:** Studies show a strong relationship between dose and serum concentration (4); however, there is a modest relationship of clinical response or risk of developing long-term side effects to either dose or serum concentration. A therapeutic window exists for haloperidol; patients who respond at serum concentrations between 5 to 16 ng/mL show no additional improvement at concentrations >16 to 20 ng/mL.(3,5) Some patients may respond at concentrations <5 ng/mL, and others may require concentrations significantly >20 ng/mL before an adequate response is attained. Because of such inter-individual variation, the serum concentration should only be used as 1 factor in determining the appropriate dose and must be interpreted in conjunction with the clinical status. Although the metabolite, reduced haloperidol, has minimal pharmacologic activity, evidence has been presented suggesting that an elevated ratio of reduced haloperidol-to-haloperidol (ie, >5) is predictive of a poor clinical response.(3,6) A reduced haloperidol-to-haloperidol ratio <0.5 indicates noncompliance; the metabolite does not accumulate except during steady-state conditions.

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<tr>
<td>REDUCED HALOPERIDOL</td>
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**Clinical References:**

**Hamster Epithelium, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical
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Hantavirus Antibody (IgG, IgM)

Interpretation: This assay detects antibodies against recombinant Hantavirus antigens of both old world and new world Hantavirus types. The immune response to Hantavirus infection is not type-specific, and thus cross-reactivity may occur. All Hantavirus IgM-positive samples from US residents will be sent to a Public Health Laboratory for Sin Nombre Virus (SNV)-specific IgM testing. Samples that are Hantavirus IgG positive but IgM negative will not be subjected to further type-specific testing, since the lack of IgM rules out acute infection.

Reference Values:
Reference Range: Negative

Haptoglobin, Serum

Clinical Information: Haptoglobin is an immunoglobulin-like plasma protein that binds hemoglobin. The haptoglobin-hemoglobin complex is removed from plasma by macrophages and the hemoglobin is catabolized. When the hemoglobin-binding capacity of haptoglobin is exceeded, hemoglobin passes through the renal glomeruli, resulting in hemoglobinuria. Chronic intravascular hemolysis causes persistently low haptoglobin concentration. Regular strenuous exercise may cause sustained low haptoglobin, presumably from low-grade hemolysis. Low serum haptoglobin may also be
due to severe liver disease. Neonatal plasma or serum specimens usually do not contain measurable haptoglobin; adult levels are achieved by 6 months. Increase in plasma haptoglobin concentration occurs as an acute-phase reaction. Levels may appear to be increased in conditions such as burns and nephrotic syndrome. An acute-phase response may be confirmed and monitored by assay of other acute-phase reactants such as alpha-1-antitrypsin and C-reactive protein.

**Useful For:** Confirmation of intravascular hemolysis

**Interpretation:** Absence of plasma haptoglobin may therefore indicate intravascular hemolysis. However, congenital anhaptoglobinemia is common, particularly in African-Americans. For this reason, it may be difficult or impossible to interpret a single measurement of plasma haptoglobin. If the assay value is low, the test should be repeated after 1 to 2 weeks following an acute episode of hemolysis. If all the plasma haptoglobin is removed following an episode of intravascular hemolysis, and if hemolysis ceases, the haptoglobin concentration should return to normal in a week. Low levels of plasma haptoglobin may indicate intravascular hemolysis.

**Reference Values:**
30-200 mg/dL

**Clinical References:**

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**Hazelnut-Food, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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HDL Cholesterol Subclasses

Reference Values:
- HDL-2 cholesterol: 9 - 38 mg/dL
- HDL-3 cholesterol: 22 - 35 mg/dL

Heavy Metal Occupational Exposure, with Reflex, Urine

Clinical Information: Arsenic (As), lead (Pb), cadmium (Cd), and mercury (Hg) are well-known toxins and toxic exposures are characterized by increased urinary excretion of these metals. Arsenic exists in a number of different forms; some are toxic while others are not. Toxic forms, which are typically encountered as a result of an industrial exposure, are the inorganic species As (+3) (As-III) and As (+5) (As-V) and the partially detoxified metabolites, monomethylarsine and dimethylarsine. The 2 most common nontoxic forms are arsenobetaine and arsenocholine. Arsenic toxicity affects a number of organ systems. Lead toxicity primarily affects the gastrointestinal, neurologic, and hematopoietic systems. Chronic exposure to cadmium causes accumulated renal damage. Mercury is essentially nontoxic in its elemental form. However, once it is chemically modified to the ionized, inorganic species, Hg(+), it becomes toxic. Further bioconversion to an alkyl mercury, such as methyl Hg (CH[3]Hg[+]), yields a species of mercury that is highly selective for lipid-rich tissue, such as the myelin sheath, and is very toxic.

Useful For: Preferred screening test for detection of arsenic, cadmium, mercury and lead due to occupational exposure in random urine specimens

Interpretation: Arsenic: Normally, humans consume 5 to 25 mcg of arsenic each day as part of their normal diet; therefore, normal urine arsenic output is below 35 mcg arsenic per gram creatinine (<35 mcg/g). When exposed to inorganic arsenic, the urine output may be more than 1,000 mcg/g and remain elevated for weeks. After a seafood meal (seafood contains a nontoxic, organic form of arsenic), on the other hand, the urine output of arsenic may be above 200 mcg/g, after which it will decline to below 35 mcg/g over a period of 1 to 2 days. Exposure to inorganic arsenic, the toxic form of arsenic, causes prolonged excretion of arsenic in the urine for many days. Urine excretion rates above 1,000 mcg/g indicates significant exposure. The highest value observed at Mayo Clinic was 450,000 mcg/L in a patient with severe symptoms of gastrointestinal distress, shallow breathing with classic "garlic breath," intermittent seizure activity, cardiac arrhythmias, and later onset of peripheral neuropathy. Cadmium: Cadmium excretion greater than 3.0 mcg/g creatinine indicates significant exposure to cadmium. Results greater than 15 mcg/g creatinine are considered indicative of severe exposure. Mercury: Urinary mercury (Hg) is the most reliable way to assess exposure to inorganic Hg, but the correlation between the levels of excretion in the urine and clinical symptoms is poor. Lead: Urinary excretion of less than 4 mcg/g creatinine is not associated with any significant lead exposure. Urinary excretion of more than 4 mcg/g creatinine is usually associated with pallor, anemia, and other evidence of lead toxicity.

Reference Values:
- ARSENIC:
  Biological Exposure Indices (BEI): <35 mcg/L at end of work week
- CADMIUM:
  Biological Exposure Indices (BEI): <5.0 mcg/g creatinine
- MERCURY:
  Biological Exposure Index (BEI): <35 mcg/g creatinine
- LEAD:
  Biological Exposure Index (BEI): <150 mcg/g creatinine

Heavy Metal/Creatinine Ratio, with Reflex, Urine

Clinical Information: Arsenic (As), lead (Pb), cadmium (Cd), and mercury (Hg) are well-known toxins and toxic exposures are characterized by increased urinary excretion of these metals. Arsenic exists in a number of different forms; some are toxic while others are not. Toxic forms, which are typically encountered as a result of an industrial exposure, are the inorganic species As (+3) (As-III) and As (+5) (As-V) and the partially detoxified metabolites, monomethylarsine and dimethylarsine. The 2 most common nontoxic forms are arsenobetaine and arsenocholine. Arsenic toxicity affects a number of organ systems. Lead toxicity primarily affects the gastrointestinal, neurologic, and hematopoietic systems. Chronic exposure to cadmium causes accumulated renal damage. Mercury is essentially nontoxic in its elemental form. However, once it is chemically modified to the ionized, inorganic species, Hg(++)+, it becomes toxic. Further bioconversion to an alkyl mercury, such as methyl Hg (CH[3]Hg[+]), yields a species of mercury that is highly selective for lipid-rich tissue, such as the myelin sheath, and is very toxic.

Useful For: Preferred screening test for detection of arsenic, cadmium, mercury, and lead in random urine specimens

Interpretation: Arsenic: Normally, humans consume 5 to 25 mcg of arsenic each day as part of their normal diet; therefore, normal urine arsenic output is less than 35 mcg arsenic per gram creatinine (<35 mcg/g). When exposed to inorganic arsenic, the urine output may be above 1,000 mcg/g and remain elevated for weeks. After a seafood meal (seafood contains a nontoxic, organic form of arsenic), on the other hand, the urine output of arsenic may be above 200 mcg/g, after which it will decline to below 35 mcg/g over a period of 1 to 2 days. Exposure to inorganic arsenic, the toxic form of arsenic, causes prolonged excretion of arsenic in the urine for many days. Urine excretion rates above 1,000 mcg/g indicate significant exposure. The highest value observed at Mayo Clinic was 450,000 mcg/L in a patient with severe symptoms of gastrointestinal distress, shallow breathing with classic "garlic breath," intermittent seizure activity, cardiac arrhythmias, and later onset of peripheral neuropathy. Cadmium: Cadmium excretion above 3.0 mcg/g creatinine indicates significant exposure to cadmium. Results above 15 mcg/g creatinine are considered indicative of severe exposure. Mercury: Urinary mercury (Hg) is the most reliable way to assess exposure to inorganic Hg, but the correlation between the levels of excretion in the urine and clinical symptoms is poor. Lead: Urinary excretion of less than 4 mcg/g creatinine is not associated with any significant lead exposure. Urinary excretion above 4 mcg/g creatinine is usually associated with pallor, anemia, and other evidence of lead toxicity.

Reference Values:

ARSENIC/CREATININE:
0-17 years: not established
> or =18 years: <24 mcg/g creatinine

CADMIUM/CREATININE:
0-17 years: not established
> or =18 years: <0.6 mcg/g creatinine

MERCURY/CREATININE:
0-17 years: not established
> or =18 years: <2 mcg/g creatinine

LEAD/CREATININE:
0-17 years: not established
incorporated into bone and erythrocytes, lead ultimately distributes among all tissues, with lipid-dense passage through the gastrointestinal tract. While a significant fraction of the absorbed lead is rapidly is enhanced by nutritional deficiency. The majority of the daily intake is excreted in the stool after direct is absorbed; children may absorb as much as 50% of the dietary intake, and the fraction of lead absorbed kidniy. The typical diet in the United States contributes 1 to 3 mcg of lead per day, of which 1% to 10% affected are epithelial cells of the gastrointestinal tract and epithelial cells of the proximal tubule of the kidney. The typical diet in the United States contributes 1 to 3 mcg of lead per day, of which 1% to 10% is absorbed; children may absorb as much as 50% of the dietary intake, and the fraction of lead absorbed is enhanced by nutritional deficiency. The majority of the daily intake is excreted in the stool after direct passage through the gastrointestinal tract. While a significant fraction of the absorbed lead is rapidly incorporated into bone and erythrocytes, lead ultimately distributes among all tissues, with lipid-dense


Clinical Information: Arsenic: Arsenic (As) exists in a number of toxic and nontoxic forms. The toxic forms are the inorganic species As(+5), also denoted as As(V), the more toxic As(+3), also known as As(III), and their partially detoxified metabolites, monomethylarsine (MMA) and dimethylarsine (DMA). Detoxification occurs in the liver as As(+3) is oxidized to As(+5) and then methylated to MMA and DMA. As a result of these detoxification steps, As(+3) and As(+5) are found in the urine shortly after ingestion, whereas MMA and DMA are the species that predominate more than 24 hours after ingestion. Blood concentrations of arsenic are elevated for a short time after exposure, after which arsenic rapidly disappears into tissues because if its affinity for tissue proteins. The body treats arsenic like phosphate, incorporating it wherever phosphate would be incorporated. Arsenic “disappears” into the normal body pool of phosphate and is excreted at the same rate as phosphate (excretion half-life of 12 days). The half-life of inorganic arsenic in blood is 4 to 6 hours, and the half-life of the methylated metabolites is 20 to 30 hours. Abnormal blood arsenic concentrations (>12 ng/mL) indicate significant exposure, but will only be detected immediately after exposure. Arsenic is not likely to be detected in blood specimens drawn more than 2 days after exposure because it has become integrated into nonvascular tissues. Consequently, blood is not a good specimen to screen for arsenic, although periodic blood levels can be determined to follow the effectiveness of therapy. Urine is the preferred specimen for assessment of arsenic exposure. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic (abdominal pain), diarrhea, and paresthesias of the hands and feet can occur. Lead: Lead is a heavy metal commonly found in man's environment that can be an acute and chronic toxin. Lead was banned from household paints in 1978, but is still found in paint produced for nondomestic use and in artistic pigments. Ceramic products available from noncommercial suppliers (such as local artists) often contain significant amounts of lead that can be leached from the ceramic by weak acids such as vinegar and fruit juices. Lead is found in dirt from areas adjacent to homes painted with lead-based paints and highways where lead accumulates from use of leaded gasoline. Use of leaded gasoline has diminished significantly since the introduction of nonleaded gasolines that have been required in personal automobiles since 1972. Lead is found in soil near abandoned industrial sites where lead may have been used. Water transported through lead or lead-soldered pipe will contain some lead with higher concentrations found in water that is weakly acidic. Some foods (for example: moonshine distilled in lead pipes) and some traditional home medicines contain lead. Lead expresses its toxicity by several mechanisms. It avidly inhibits aminolevulinic acid dehydratase and ferrochelatase, 2 of the enzymes that catalyze synthesis of heme; the end result is decreased hemoglobin synthesis resulting in anemia. Lead also is an electrophile that avidly forms covalent bonds with the sulfhydryl group of cysteine in proteins. Thus, proteins in all tissues exposed to lead will have lead bound to them. The most common sites affected are epithelial cells of the gastrointestinal tract and epithelial cells of the proximal tubule of the kidney. The typical diet in the United States contributes 1 to 3 mcg of lead per day, of which 1% to 10% is absorbed; children may absorb as much as 50% of the dietary intake, and the fraction of lead absorbed is enhanced by nutritional deficiency. The majority of the daily intake is excreted in the stool after direct passage through the gastrointestinal tract. While a significant fraction of the absorbed lead is rapidly incorporated into bone and erythrocytes, lead ultimately distributes among all tissues, with lipid-dense

Heavy Metals Screen with Demographics, Blood


Clinical Information: Arsenic: Arsenic (As) exists in a number of toxic and nontoxic forms. The toxic forms are the inorganic species As(+5), also denoted as As(V), the more toxic As(+3), also known as As(III), and their partially detoxified metabolites, monomethylarsine (MMA) and dimethylarsine (DMA). Detoxification occurs in the liver as As(+3) is oxidized to As(+5) and then methylated to MMA and DMA. As a result of these detoxification steps, As(+3) and As(+5) are found in the urine shortly after ingestion, whereas MMA and DMA are the species that predominate more than 24 hours after ingestion. Blood concentrations of arsenic are elevated for a short time after exposure, after which arsenic rapidly disappears into tissues because if its affinity for tissue proteins. The body treats arsenic like phosphate, incorporating it wherever phosphate would be incorporated. Arsenic “disappears” into the normal body pool of phosphate and is excreted at the same rate as phosphate (excretion half-life of 12 days). The half-life of inorganic arsenic in blood is 4 to 6 hours, and the half-life of the methylated metabolites is 20 to 30 hours. Abnormal blood arsenic concentrations (>12 ng/mL) indicate significant exposure, but will only be detected immediately after exposure. Arsenic is not likely to be detected in blood specimens drawn more than 2 days after exposure because it has become integrated into nonvascular tissues. Consequently, blood is not a good specimen to screen for arsenic, although periodic blood levels can be determined to follow the effectiveness of therapy. Urine is the preferred specimen for assessment of arsenic exposure. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic (abdominal pain), diarrhea, and paresthesias of the hands and feet can occur. Lead: Lead is a heavy metal commonly found in man's environment that can be an acute and chronic toxin. Lead was banned from household paints in 1978, but is still found in paint produced for nondomestic use and in artistic pigments. Ceramic products available from noncommercial suppliers (such as local artists) often contain significant amounts of lead that can be leached from the ceramic by weak acids such as vinegar and fruit juices. Lead is found in dirt from areas adjacent to homes painted with lead-based paints and highways where lead accumulates from use of leaded gasoline. Use of leaded gasoline has diminished significantly since the introduction of nonleaded gasolines that have been required in personal automobiles since 1972. Lead is found in soil near abandoned industrial sites where lead may have been used. Water transported through lead or lead-soldered pipe will contain some lead with higher concentrations found in water that is weakly acidic. Some foods (for example: moonshine distilled in lead pipes) and some traditional home medicines contain lead. Lead expresses its toxicity by several mechanisms. It avidly inhibits aminolevulinic acid dehydratase and ferrochelatase, 2 of the enzymes that catalyze synthesis of heme; the end result is decreased hemoglobin synthesis resulting in anemia. Lead also is an electrophile that avidly forms covalent bonds with the sulfhydryl group of cysteine in proteins. Thus, proteins in all tissues exposed to lead will have lead bound to them. The most common sites affected are epithelial cells of the gastrointestinal tract and epithelial cells of the proximal tubule of the kidney. The typical diet in the United States contributes 1 to 3 mcg of lead per day, of which 1% to 10% is absorbed; children may absorb as much as 50% of the dietary intake, and the fraction of lead absorbed is enhanced by nutritional deficiency. The majority of the daily intake is excreted in the stool after direct passage through the gastrointestinal tract. While a significant fraction of the absorbed lead is rapidly incorporated into bone and erythrocytes, lead ultimately distributes among all tissues, with lipid-dense
tissues such as the central nervous system being particularly sensitive to organic forms of lead. All absorbed lead is ultimately excreted in the bile or urine. Soft-tissue turnover of lead occurs within approximately 120 days. Avoidance of exposure to lead is the treatment of choice. However, chelation therapy is available to treat severe disease. Oral dimercaprol may be used in the outpatient setting except in the most severe cases. Cadmium: The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of chronic exposure comes from spray painting of organic-based paints without use of a protective breathing apparatus; auto repair mechanics represent a susceptible group for cadmium toxicity. In addition, another common source of cadmium exposure is tobacco smoke. Mercury: Mercury (Hg) is essentially nontoxic in its elemental form. If Hg(0) is chemically modified to the ionized, inorganic species, Hg(+2), it becomes toxic. Further bioconversion to an alkyl Hg, such as methyl Hg (CH[3]Hg(+)), yields a species of mercury that is highly selective for lipid-rich tissue such as neurons and is very toxic. The relative order of toxicity is: Not Toxic -- Hg(0) < Hg(+2) << CH(3)Hg(+) -- Very Toxic Mercury can be chemically converted from the elemental state to the ionized state. In industry, this is frequently done by exposing Hg(0) to strong oxidizing agents such as chlorine. Hg(0) can be bioconverted to both Hg(+2) and alkyl Hg by microorganisms that exist both in the normal human gut and in the bottom sediment of lakes, rivers, and oceans. When Hg(0) enters bottom sediment, it is absorbed by bacteria, fungi, and small microorganisms; they metabolically convert it to Hg(+2), CH(3)Hg(+), and (CH[3])(+2)Hg. Should these microorganisms be consumed by larger marine animals and fish, the mercury passes up the food chain in rather toxic form. Mercury expresses its toxicity in 3 ways: -Hg(+2) is readily absorbed and reacts with sulfhydryl groups of protein, causing a change in the tertiary structure of the protein—a stereoisomeric change—with subsequent loss of the unique activity associated with that protein. Because Hg(+2) becomes concentrated in the kidney during the regular clearance processes, this target organ experiences the greatest toxicity. -With the tertiary change noted previously, some proteins become immunogenic, eliciting a proliferation of T lymphocytes that generate immunoglobulins to bind the new antigen; collagen tissues are particularly sensitive to this. -Alkyl Hg species, such as CH(3)Hg(+), are lipophilic and avidly bind to lipid-rich tissues such as neurons. Myelin is particularly susceptible to disruption by this mechanism. Members of the public will occasionally become concerned about exposure to mercury from dental amalgams. Restorative dentistry has used a mercury-silver amalgam for approximately 90 years as a filling material. A small amount of mercury (2-20 mcg/day) is released from a dental amalgam when it was mechanically manipulated, such as by chewing. The habit of gum chewing can cause release of mercury from dental amalgams greatly above normal. The normal bacterial flora present in the mouth converts a fraction of this to Hg(+2) and CH(3)Hg(+), which was shown to be incorporated into body tissues. The World Health Organization safety standard for daily exposure to mercury is 45 mcg/day. Thus, if one had no other source of exposure, the amount of mercury released from dental amalgams is not significant.(1) Many foods contain mercury. For example, commercial fish considered safe for consumption contain <0.3 mcg/g of mercury, but some game fish contain >2.0 mcg/g and, if consumed on a regular basis, contribute to significant body burdens. Therapy is usually monitored by following urine output; therapy may be terminated after urine excretion is <50 mcg/day.

Useful For: Detecting exposure to arsenic, lead, cadmium, and mercury

Interpretation: Arsenic: Abnormal blood arsenic concentrations (>12 ng/mL) indicate significant exposure. Absorbed arsenic is rapidly distributed into tissue storage sites with a blood half-life of ~6 hours. Unless a blood specimen is drawn within 2 days of exposure, arsenic is not likely to be detected in a blood specimen. Lead: The 95th percentile of the Gaussian distribution of whole blood lead concentration in a population of unexposed adults is <6.0 mcg/dL. For pediatric patients, there may be an association with blood lead values of 5.0 to 9.9 mcg/dL and adverse health effects. Follow-up testing in 3 to 6 months may be warranted. Chelation therapy is indicated when whole blood lead concentration is >25.0 mcg/dL in children or >45.0 mcg/dL in adults. The Occupational Safety and Health Administration has published the following standards for employees working in industry: -Employees with a single whole blood lead result >60.0 mcg/dL must be removed from workplace exposure. -Employees with whole blood lead levels >50.0 mcg/dL averaged over 3 blood samplings must be removed from workplace exposure. -An employee may not return to work in a lead exposure environment until their whole blood lead level is <40 mcg/dL. New York State has mandated inclusion of the following statement in reports for children under the age of 6 with blood lead in the range of 5.0
to 9.9 mcg/dL: "Blood lead levels in the range of 5.0-9.9 mcg/dL have been associated with adverse health effects in children aged 6 years and younger." Cadmium: Normal blood cadmium is <5.0 ng/mL, with most results in the range of 0.5 to 2.0 ng/mL. Acute toxicity will be observed when the blood level exceeds 50 ng/mL. Mercury: The quantity of mercury (Hg) found in blood and urine correlates with degree of toxicity. Hair analysis can be used to document the time of peak exposure if the event was in the past. Normal whole blood mercury is usually <10 ng/mL. Individuals who have mild exposure during work, such as dentists, may routinely have whole blood mercury levels up to 15 ng/mL. Significant exposure is indicated when the whole blood mercury is >50 ng/mL if exposure is due to alkyl Hg, or >200 ng/mL if exposure is due to Hg(+2).

Reference Values:
ARSENIC
0-12 ng/mL
Reference values apply to all ages.

LEAD
All ages: 0.0-4.9 mcg/dL
Critical values
Pediatrics (< or =15 years): > or =20.0 mcg/dL
Adults (> or =16 years): > or =70.0 mcg/dL.

CADMIUM
0.0-4.9 ng/mL
Reference values apply to all ages.

MERCURY
0-9 ng/mL
Reference values apply to all ages.

Clinical References:

Heavy Metals Screen, with Reflex, 24 Hour, Urine

Clinical Information: Arsenic: Arsenic is perhaps the best known of the metal toxins, having gained notoriety from its extensive use by Renaissance nobility as an antisyphilitic agent and, paradoxically, as an antidote against acute arsenic poisoning. Even today, arsenic is still 1 of the more common toxicants found in insecticides, and leaching from bedrock to contaminate groundwater. The toxicity of arsenic is due to 3 different mechanisms, 2 of them related to energy transfer. Arsenic covalently and avidly binds to dihydrolipoic acid, a necessary cofactor for pyruvate dehydrogenase. Absence of the cofactor inhibits the conversion of pyruvate to acetyl coenzyme A, the first step in gluconeogenesis. This results in loss of energy supply to anaerobic cells, the predominant mechanism of action of arsenic on neural cells that rely on anaerobic respiration for energy. Neuron cell destruction that occurs after long-term energy loss results
in bilateral peripheral neuropathy. Arsenic also competes with phosphate for binding to adenosine triphosphate during its synthesis by mitochondria via oxidative phosphorylation, causing formation of the lower energy adenosine diphosphate monoarsine. This results in loss of energy supply to aerobic cells. Cardiac cells are particularly sensitive to this form of energy loss; fatigue due to poor cardiac output is a common symptom of arsenic exposure. Arsenic furthermore binds avidly with any hydrated sulfhydryl group on protein, distorting the 3-dimensional configuration of that protein, causing it to lose activity. Interaction of arsenic with epithelial cell protein at the sites of highest physiologic concentration, the small intestine and proximal tubule of the kidney, results in cellular degeneration. Epithelial cell erosion in the gastrointestinal tract and proximal tubule are characteristic of arsenic toxicity. Arsenic is also a known carcinogen, but the mechanism of this effect is not definitively known. A wide range of signs and symptoms may be seen in acute arsenic poisoning including headache, nausea, vomiting, diarrhea, abdominal pain, hypotension, fever, hemolysis, seizures, and mental status changes. Symptoms of chronic poisoning, also called arseniasis, are mostly insidious and nonspecific. The gastrointestinal tract, skin, and central nervous system are usually involved. Nausea, epigastric pain, colic abdominal pain, diarrhea, and paresthesias of the hands and feet can occur. Arsenic exists in a number of different forms; organic forms are nontoxic, inorganic forms are toxic. See ASFR / Arsenic Fractionation, 24 Hour, Urine for details about arsenic forms. Because arsenic is excreted predominantly by glomerular filtration, analysis for arsenic in urine is the best screening test to detect arsenic exposure. Cadmium: The toxicity of cadmium resembles the other heavy metals (arsenic, mercury, and lead) in that it attacks the kidney; renal dysfunction with proteinuria with slow onset (over a period of years) is the typical presentation. Measurable changes in proximal tubule function, such as decreased clearance of para-aminohippuric acid, also occur over a period of years, and precede overt renal failure. Breathing the fumes of cadmium vapors leads to nasal epithelial deterioration and pulmonary congestion resembling chronic emphysema. The most common source of chronic exposure comes from spray painting of organic-based paints without use of a protective breathing apparatus; auto repair mechanics represent a susceptible group for cadmium toxicity. Another common source of cadmium exposure is tobacco smoke, which has been implicated as the primary source of the metal leading to reproductive toxicity in both males and females. The concentration of cadmium in the kidneys and in the urine is elevated in some patients exposed to cadmium. Mercury: The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor. However, urinary Hg is the most reliable way to assess exposure to inorganic Hg. For additional information, see HG / Mercury, Blood Lead: Increased urine lead excretion rate indicates significant lead exposure. Measurement of urine lead excretion rate before AND after chelation therapy has been used as an indicator of lead exposure. An increase in lead excretion rate in the post chelation specimen of up to 6 times the rate in the prechelation specimen is normal. Blood lead is the best clinical correlate of toxicity. For additional information, see PBDB / Lead with Demographics, Blood.

Useful For: Detecting arsenic, cadmium, mercury, and lead exposure and toxicity in 24-hour urine specimen

Interpretation: Arsenic: Normally, humans consume 5 to 25 mcg of arsenic each day as part of their normal diet; therefore, normal urine arsenic output is less than 25 mcg/specimen. After a seafood meal (seafood contains a nontoxic, organic form of arsenic), the urine output of arsenic may increase to 300 mcg/specimen for 1 day, after which it will decline to less than 25 mcg/specimen. Exposure to inorganic arsenic, the toxic form of arsenic, causes prolonged excretion of arsenic in the urine for many days. Urine excretion rates greater than 1,000 mcg/specimen indicate significant exposure. The highest level observed at Mayo Clinic was 450,000 mcg/specimen in a patient with severe symptoms of gastrointestinal distress, shallow breathing with classic "garlic breath," intermittent seizure activity, cardiac arrhythmias, and later onset of peripheral neuropathy. Cadmium: In chronic cadmium exposure, the kidneys are the primary target organ. Urine concentrations of cadmium can be useful to assess long-term exposure and determine cadmium body burden. Collection of urine over 24 hours minimizes fluctuations of observed cadmium concentrations in random urine samples. Mercury: Daily urine excretion of mercury above 50 mcg/day indicates significant exposure (per World Health Organization standard). Lead: Urinary excretion of less than 125 mcg of lead per 24 hours is not associated with any significant lead exposure. Urinary excretion of more than 125 mcg of lead per 24 hours is usually associated with pallor, anemia, and other evidence of lead toxicity.

Reference Values:

ARSENIC:
Heavy Metals, Hair

Clinical Information: ARSENIC Arsenic circulating in the blood will bind to protein by formation of a covalent complex with sulfhydryl groups of the amino acid cysteine. Keratin, the major structural protein in hair and nails, contains many cysteine residues and, therefore, is one of the major sites for accumulation of arsenic. Since arsenic has a high affinity for keratin, the concentration of arsenic in hair is higher than in other tissues. Arsenic binds to keratin at the time of exposure, “trapping” the arsenic in hair. Therefore, hair analysis for arsenic is not only used to document that an exposure occurred, but when it occurred. Hair collected from the nape of the neck can be used to document recent exposure. Axillary or pubic hair are used to document long-term (6 months-1 year) exposure. MERCURY Once absorbed and circulating, mercury becomes bound to numerous proteins, including keratin. The concentration of mercury in hair correlates with the severity of clinical symptoms. If the hair can be segregated by length, such an exercise can be useful in identifying the time of exposure. LEAD Hair analysis for lead can be used to corroborate blood analysis or to document past lead exposure. If the hair is collected and segmented in a time sequence (based on length from root), the approximate time of exposure can be assessed.

Useful For: Detection of nonacute arsenic, mercury, and lead exposure in hair specimens

Interpretation: Hair grows at a rate of approximately 0.5 inch/month. Hair keratin synthesized today will protrude through the skin in approximately 1 week. Thus, a hair specimen collected at the skin level represents exposure of 1 week ago, 1 inch distally from the skin represents exposure 2 months ago, etc. ARSENIC Hair arsenic levels above 1.00 mcg/g dry weight indicate excessive exposure. It is normal for some arsenic to be present in hair, as everybody is exposed to trace amounts of arsenic from the normal diet. The highest hair arsenic observed at Mayo Clinic was 210 mcg/g dry weight in a case of chronic exposure that was the cause of death. MERCURY Normally, hair contains less than 1 mcg/g of mercury; any amount more than this indicates that exposure to more than normal amounts of mercury has occurred. LEAD Normal hair lead content is below 5.0 mcg/g. Hair lead content above 10.0 mcg/g indicates significant lead exposure.

Reference Values:

ARSENIC
0-15 years: not established
> or =16 years: 0.0-0.9 mcg/g of hair

LEAD
0.0-3.9 mcg/g of hair
Reference values apply to all ages.
MERCURY
0-15 years: not established
> or =16 years: 0.0-0.9 mcg/g of hair


Heavy Metals, Nails

Clinical Information: ARSENIC Arsenic circulating in the blood will bind to protein by formation of a covalent complex with sulfhydryl groups of the amino acid cysteine. Keratin, the major structural protein in hair and nails, contains many cysteine residues and, therefore, is one of the major sites for accumulation of arsenic. Since arsenic has a high affinity for keratin, the concentration of arsenic in nails is higher than in other tissues. Several weeks after exposure, transverse white striae, called Mees' lines, may appear in the fingernails MERCURY Once absorbed and circulating, mercury becomes bound to numerous proteins, including keratin. The concentration of mercury in nails correlates with the severity of clinical symptoms. If the nails can be segregated by length, such an exercise can be useful in identifying the time of exposure. LEAD Nail analysis of lead can be used to corroborate blood analysis.

Useful For: Detection of nonacute arsenic, mercury, and lead exposure

Interpretation: Nails grow at a rate of approximately 0.1 inch/month. Nail keratin synthesized today will grow to the distal end in approximately 6 months. Thus, a nail specimen collected at the distal end represents exposure of 6 months ago. ARSENIC Nail arsenic above 1.0 mcg/g dry weight indicates excessive exposure. It is normal for some arsenic to be present in nails, as everybody is exposed to trace amounts of arsenic from the normal diet. The highest hair or nail arsenic observed at Mayo Clinic was 210 mcg/g dry weight in a case of chronic exposure that was the cause of death. MERCURY Normally, nails contain less than 1 mcg/g of mercury; any amount above this indicates that exposure to more than normal amounts of mercury has occurred. LEAD: Normally, the nail lead content is below 4.0 mcg/g. Nail lead content above 10.0 mcg/g indicates significant lead exposure.

Reference Values:
ARSENIC
0-15 years: not established
> or =16 years: 0.0-0.9 mcg/g of nails

LEAD
0.0-3.9 mcg/g of nails
Reference values apply to all ages.

MERCURY
0-15 years: not established
> or =16 years: 0.0-0.9 mcg/g of nails


**Helicobacter pylori (H pylori) Immunostain, Technical Component Only**

**Clinical Information:** Helicobacter pylori is a bacterium that frequently infects the stomach, colonizing the gastric pits. H pylori infection is associated with the development of gastroduodenal ulcers and gastric mucosa-associated lymphoid tissue (MALT) lymphomas.

**Useful For:** Aids in the identification of Helicobacter pylori infection

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Helicobacter pylori Antigen, Feces**

**Clinical Information:** Helicobacter pylori is well recognized as the cause of chronic active gastritis, duodenal ulcer, and nonulcer dyspepsia. Currently accepted methods for the diagnosis of Helicobacter pylori infection include the urea breath test (UBT / Helicobacter pylori Breath Test) and culture or histologic examination or direct urease testing of biopsy specimens obtained at the time of gastroduodenoscopy. Each of these tests has its drawbacks, including lack of specificity (serology) or high cost, complexity, and inconvenience for the patient. The utility of this test in asymptomatic individuals is not known, but testing for Helicobacter pylori in such individuals is not generally recommended. See Helicobacter pylori Diagnostic Algorithm in Special Instructions.

**Useful For:** Aiding in the diagnosis of Helicobacter pylori infection Monitoring the eradication of Helicobacter pylori after therapy (in most situations, confirmation of eradication is not mandatory)

**Interpretation:** Positive results indicate the presence of Helicobacter pylori antigen in the stool. Negative results indicate the absence of detectable antigen, but does not eliminate the possibility of infection due to Helicobacter pylori.

**Reference Values:**
Negative

Helicobacter pylori Breath Test

Clinical Information: The causal relationship between the urease-producing bacterium, Helicobacter pylori, and chronic active gastritis, duodenal ulcer, and nonulcer dyspepsia is well established. Conventional methods for the diagnosis of active H pylori infection include evaluation of biopsied gastric tissue by histopathology and culture. Less invasive assays include testing for the presence of H pylori antigen in stool specimens and detection of H pylori urease production by the Urea Breath Test (UBT). Serologic testing for the presence of IgM/IgG/IgA-class antibodies to H pylori is also performed; however, this is not recommended by either the American College of Gastroenterologists or the American Gastroenterological Association (AGA) as an accurate marker for active disease. These serologic markers can remain elevated despite resolution of active disease and may lead to misdiagnosis and inappropriate treatment. Recommendations for use of the (13)C-Urea Breath Test (Meretek UBT) were recently provided by the Digestive Health Initiative, a joint committee assembled with representatives from the AGA, the American Society for Gastrointestinal Endoscopy (ASGE), and the American Association for the Study of Liver Diseases (AASLD). These recommendations include the following statements: "When endoscopy is not clinically indicated, the primary diagnosis of H pylori infection can be made serologically or with the UBT. When endoscopy is clinically indicated, the primary diagnosis should be established by biopsy urease testing and/or histology. Available evidence suggests that confirmation of H pylori eradication is not mandatory in most situations because of costs associated with testing. However, for selected patients with complicated ulcer disease, low-grade gastric mucosa-associated lymphoid tissue lymphoma, and following resection of early gastric cancer, it is appropriate to confirm eradication. In other situations, the decision to confirm H pylori eradication should be made on a case-by-case basis." This consensus group further specifies that there is no indication to test asymptomatic people and that testing for H pylori is only recommended if treatment is planned. The (13)C-Urea Breath Test (Meretek UBT) is a highly sensitive and specific noninvasive, nonradioactive test for diagnosing H pylori infection prior to antimicrobial treatment and for assessing whether the organism has been successfully eradicated following antimicrobial therapy. In 2 recent large prospective studies, the (13)C-UBT was shown to be as, or more, sensitive and specific for diagnosing H pylori active infection than culture, PCR, stain, rapid urease testing of biopsy tissue, or serology. When the test is used to assess eradication, it should be performed 4 to 6 weeks after completion of antimicrobial treatment. See Helicobacter pylori Diagnostic Algorithm in Special Instructions.

Useful For: Diagnostic testing for Helicobacter pylori infection in patients suspected to have active H pylori infection Monitoring response to therapy

Interpretation: The Helicobacter pylori urea breath test can detect very low levels of H pylori and, by assessing the entire gastric mucosa, avoids the risk of sampling errors inherent in biopsy-based methods. In the absence of gastric H pylori, the (13)C-urea does not produce (13)CO2 in the stomach. A negative result does not rule out the possibility of H pylori infection. If clinical signs are suggestive of H pylori infection, retest with a new specimen or by using an alternative method. A false-positive test may occur due to urease associated with other gastric spiral organisms observed in humans such as H heilmannii. A false-positive test could occur in patients who have achlorhydria.

Reference Values:
Negative
Reference values apply to all ages.

Helicobacter pylori-associated disease, the noninvasive stool antigen or urea breath test is recommended. If patients fail to respond to treatment and antimicrobial resistance is suspected, a gastric biopsy, gastric brushings, or gastric aspirate may be cultured to attempt to recover the organism for antimicrobial susceptibility testing to assess for resistance.

**Useful For:** Recovery of Helicobacter pylori from gastric specimens for antimicrobial susceptibility testing of the organism

**Interpretation:** A positive result provides definitive evidence of the presence of Helicobacter pylori. Organisms may be detected in asymptomatic (colonized) individuals. False-negative culture results may occur since the organism may die between biopsy collection and laboratory culture.

**Reference Values:**
No growth after 7 days


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**Helicobacter pylori Culture with Antimicrobial Susceptibilities**

**Clinical Information:** Helicobacter pylori is a spiral-shaped gram-negative bacterium that may cause chronic gastritis, peptic ulcer disease, or gastric neoplasia. In adults of industrialized countries, an estimated 0.5% of the susceptible population becomes infected each year, although the incidence has been decreasing over time. The organism may asymptomatically colonize humans. In suspected H pylori-associated disease, the noninvasive stool antigen or urea breath test is recommended. If patients fail to respond to treatment and antimicrobial resistance is suspected, gastric biopsy, gastric brushings, or gastric aspirate may be cultured to attempt to recover the organism for antimicrobial susceptibility testing to assess for resistance. Multidrug regimens are required to attain successful cure of H pylori infection. Antimicrobial resistance in H pylori is increasing. Disease caused by H pylori resistant to clarithromycin or metronidazole is associated with a greater incidence of treatment failure than disease caused by a susceptible strain. The Clinical and Laboratory Standards Institute (CLSI) recommends agar dilution for H pylori antimicrobial susceptibility testing. Amoxicillin, ciprofloxacin, clarithromycin, metronidazole and tetracycline are routinely tested. The only antimicrobial for which interpretive breakpoints have been defined by the CLSI is clarithromycin.

**Useful For:** Recovery of Helicobacter pylori from gastric specimens for antimicrobial susceptibility testing of the organism (amoxicillin, ciprofloxacin, clarithromycin, metronidazole and tetracycline are routinely tested)

**Interpretation:** A positive result provides definitive evidence of the presence of Helicobacter pylori. Organisms may be detected in asymptomatic (colonized) individuals. False-negative culture results may occur since the organism may die between biopsy collection and laboratory culture.

**Reference Values:**
No growth after 7 days

Susceptibility results are reported as minimum inhibitory concentration (MIC) in mcg/mL and as susceptible, intermediate, or resistant according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.

In some instances an interpretive category cannot be provided based on available data and the following comment will be included: "There are no established interpretive guidelines for agents reported without interpretations."

**Susceptible (S):**
The "susceptible" category implies that isolates are inhibited by the usually achievable concentrations of antimicrobial agent when the dosage recommended to treat the site of infection is used, resulting in likely clinical efficacy.

**Intermediate (I):**
The "intermediate" category includes isolates with antimicrobial agent minimum inhibitory
concentrations (MICs) that approach usually attainable blood and tissue levels, and for which response rates may be lower than for susceptible isolates.

Note: The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated or when a higher than normal dosage of a drug can be used. This category also includes a buffer zone, which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.

Resistant (R)

The "resistant" category implies that the isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or that demonstrate MIC that fall in the range where specific microbial resistance mechanisms are likely, and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.

(Clinical and Laboratory Standards Institute: Performance Standards for Antimicrobial Susceptibility Testing. 26th Informational Supplement. CLSI document M100S. Wayne, PA, 2016)


Helminthosporium halodes, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

FHSSE 57532 Helminthosporium sativum/Drechslera IgE

Interpretation: Class IgG (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:
<0.35 kU/L

HOLDC 35848 Hematologic Disorders, Chromosome Hold, Bone Marrow or Peripheral Blood

Clinical Information: Conventional chromosome analysis is the gold standard for identification of the common, recurrent chromosome abnormalities for most hematologic malignancies. Based on morphologic review of the bone marrow or peripheral blood specimen by a hemopathologist, a determination of additional appropriate testing can be made. If the specimen does not show evidence of malignancy, chromosome analysis may not be necessary. Depending on the diagnosis, FISH assays may also be more informative.

Useful For: Holding the bone marrow or peripheral blood specimen in the laboratory but delaying chromosome analysis while preliminary morphologic assessment is in process

Interpretation: If notified by the client, this test may be canceled and a processing fee assessed. If no notification to cancel testing is received, this test will be reported as "reflexed for chromosome analysis" and depending on the specimen received, CHRBM / Chromosome Analysis, Hematologic Disorders, Bone Marrow or CHRHFB / Chromosome Analysis, Hematologic Disorders, Blood will be performed and an interpretive report provided.

Reference Values:
Not applicable

EXHR 65114 Hematologic Disorders, DNA and RNA Extract and Hold

Clinical Information: It is frequently useful to obtain nucleic acid from clinical samples containing a hematopoietic neoplasm at the time of diagnosis, so that appropriate material is available for molecular analysis should subsequent testing be required. For example, when a diagnosis of acute myelogenous leukemia is made, there is a delay before karyotype information, which determines whether testing for molecular prognostic markers is necessary, is available. After this delay, the diagnostic sample is usually no longer available or the nucleic acid has degraded to such an extent that it is no longer adequate for testing. Thus, it is useful to obtain nucleic acid on such specimens promptly at diagnosis and retain it until it is known whether additional testing is necessary.

Useful For: Reserving nucleic acid on any specimen for which molecular analysis requiring DNA or RNA may be necessary at a future date, ensuring that adequate material for testing is available

Interpretation: A report of "Performed" will be sent and a $75 processing fee will be assessed. No interpretation will be given. Should the sample be used in future testing, interpretation would be incorporated with the final testing.

Reference Values:
Not applicable
Hematologic Disorders, DNA Extract and Hold

**Clinical Information:** It is frequently useful to obtain nucleic acid from clinical samples containing a hematopoietic neoplasm at the time of diagnosis, so that appropriate material is available for molecular analysis should subsequent testing be required. For example, when a diagnosis of acute myelogenous leukemia is made, there is a delay before karyotype information, which determines whether testing for molecular prognostic markers is necessary, is available. After this delay, the diagnostic sample is usually no longer available or the nucleic acid has degraded to such an extent that it is no longer adequate for testing. Thus, it is useful to obtain nucleic acid on such specimens promptly at diagnosis and retain it until it is known whether additional testing is necessary.

**Useful For:** Reserving nucleic acid on any specimen for which molecular analysis requiring DNA may be necessary at a future date, ensuring that adequate material for testing is available

**Interpretation:** A report of "Performed" will be sent and a $50 processing fee will be assessed. No interpretation will be given. Should the sample be used in future testing, interpretation would be incorporated with the final testing.

**Reference Values:**
Not applicable

Hematologic Disorders, Fluorescence In Situ Hybridization (FISH) Hold, Bone Marrow or Peripheral Blood

**Clinical Information:** FISH analysis using gene-specific probes is a useful methodology to detect common, recurrent chromosome abnormalities for most hematologic malignancies. Based on morphologic review of the bone marrow or peripheral blood specimen by a hematopathologist, a determination of additional appropriate testing can be made. If the specimen does not show evidence of malignancy, FISH analysis may not be necessary. Depending on the diagnosis, conventional chromosome analysis may also be more informative.

**Useful For:** Processing the bone marrow or peripheral blood specimen but delaying FISH analysis while preliminary morphologic assessment is in process

**Interpretation:** If notified by the client, this test may be canceled and a processing fee will be assessed. If no notification to proceed with testing is received, this test will be reported as "canceled."

**Reference Values:**
Not applicable

Hematologic Disorders, Leukemia/Lymphoma; Flow Hold, Varies

**Clinical Information:** Diagnostic hematopathology has become an increasingly complex subspecialty, particularly with neoplastic disorders of blood and bone marrow. While morphologic assessment of blood smears, bone marrow smears, and tissue sections remains the cornerstone of lymphoma and leukemia diagnosis and classification, immunophenotyping is a very valuable and important complementary tool. Immunophenotyping hematopoietic specimens can help resolve many differential diagnostic problems posed by the clinical or morphologic features.

**Useful For:** Evaluating lymphocytoses of undetermined etiology Identifying B- and T-cell lymphoproliferative disorders involving blood and bone marrow Distinguishing acute lymphoblastic leukemia (ALL) from acute myeloid leukemia (AML) Immunologic subtyping of ALL Distinguishing reactive lymphocytes and lymphoid hyperplasia from malignant lymphoma Distinguishing between malignant lymphoma and acute leukemia Phenotypic subclassification of B- and T-cell chronic lymphoproliferative disorders, including chronic lymphocytic leukemia, mantle cell lymphoma, and
hairy cell leukemia Recognizing AML with minimal morphologic or cytochemical evidence of differentiation Recognizing monoclonal plasma cells

**Interpretation:** Report will include a morphologic description, a summary of the procedure, the percent positivity of selected antigens, and an interpretive conclusion based on the correlation of the clinical history with the morphologic features and immunophenotypic results.

**Reference Values:**
When performed, an interpretive report will be provided.
This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and correlation with the morphologic features will be provided by a hematopathologist.

**Clinical References:**

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**P53CA Hematologic Neoplasms, TP53 Somatic Mutation, DNA Sequencing Exons 4-9**

**Clinical Information:** Patients with chronic lymphocytic leukemia (CLL) have variable disease course influenced by a series of tumor biologic factors. The presence of chromosomal 17p- or TP53 gene mutation confers a very poor prognosis to a subset of CLL patients, both at time of initial diagnosis, as well as at disease progression, or in the setting of therapeutic resistance. TP53 gene mutation status in CLL has emerged as the single most predictive tumor genetic abnormality associated with adverse outcome and poor response to standard immunochemotherapy; however, patients can be managed with alternative therapeutic options. Although the prognostic relevance of acquired TP53 gene mutation is best studied for CLL, similar findings are also reported for other hematologic malignancies including low-grade B-cell lymphoma, diffuse large B-cell lymphoma, and some types of myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). Therefore, while this test has been developed to be primarily focused on high-risk CLL patients, p53 gene sequencing analysis can also be performed in additional neoplasms, as clinically indicated.

**Useful For:** Evaluating chronic lymphocytic leukemia patients at diagnosis or during disease course for the presence of TP53 gene mutations indicating high risk of disease progression and adverse outcomes

**Interpretation:** Results are reported in standard nomenclature according to the most recent Human Genome Variation Society (HGVS) recommendations and an interpretive comment regarding the nature of the mutation (eg, known deleterious, suspected deleterious, synonymous change) will be included to complete the clinical report.

**Reference Values:**
Mutations present or absent as compared to a reference sequence of the normal TP53 gene

**Clinical References:**
associated with poor prognosis in chronic lymphocytic leukemia: results from a detailed genetic
chronic lymphocytic leukemia is independent of Del17p13: implications for overall survival and
on risk-stratified management for chronic lymphocytic leukemia. Leuk Lymphoma 2006;47(9):1738-1746
et al: Missense mutations located in structural p53 DNA-binding motifs are associated with extremely
predict clinical outcome in diffuse large B-cell lymphoma: an international collaborative study. Blood
2008;112:3088-3098
in-house cases.

**Useful For:** Obtaining a rapid, expert opinion on unprocessed specimens referred by the primary pathologist Obtaining special studies not available locally

**Interpretation:** Results of the consultation are reported in a formal pathology report that includes a description of ancillary test results (if applicable) and an interpretive comment. When the case is completed, results may be communicated by a phone call. In our consultative practice, we strive to bring the physician and patient the highest quality of diagnostic pathology, in all areas of expertise, aiming to utilize only those ancillary tests that support the diagnosis in a cost-effective manner, and to provide a rapid turnaround time for diagnostic results.

**Reference Values:**
The laboratory will provide a pathology consultation.

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**FHME** 57485

Hemiplegic Migraine Sequencing Evaluation

**Clinical Information:** Detects sequence variants in the CACNA1A, ATP1A2 and SCN1A genes in patients with migraine, migraine with aura, reversible hemiparesis, atypical migraine, and family history of migraine, seizures.

**Reference Values:**
A final report will be attached in MayoAccess.

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**HFE** 35455

Hemochromatosis HFE Gene Analysis, Blood

**Clinical Information:** Hereditary hemochromatosis (HH) is an autosomal recessive disorder of iron metabolism with a carrier frequency of approximately 1 in 10 individuals of northern European ancestry. The disease is characterized by an accelerated rate of intestinal iron absorption and progressive iron deposition in various tissues. Iron overload can cause hepatic cirrhosis, hepatocellular carcinoma, diabetes mellitus, arthropathy, and cardiomyopathy. Such complications can generally be prevented by phlebotomy, and patients have a normal life expectancy if treated before organ damage occurs. For individuals with clinical symptoms consistent with HH or biochemical evidence of iron overload, an HH diagnosis is typically based on the results of transferrin-iron saturation and serum ferritin concentration. Molecular testing can be done to confirm the diagnosis. The majority of HH patients have mutations in the HFE gene. Clinically significant iron overload also can occur in the absence of known HFE mutations, so a negative HFE test does not exclude a diagnosis of iron overload or hemochromatosis. The most common mutation in the HFE gene is C282Y (exon 4, 845G->A). Homozygosity for the C282Y mutation is associated with 60% to 90% of all cases of HH. Additionally, 3% to 8% of individuals affected with HH are heterozygous for this mutation. These frequencies show variability among different populations, with the highest frequency observed in individuals of northern European ancestry. Penetrance for elevated serum iron indices among C282Y homozygotes is relatively high, but not 100%. However, the penetrance for the characteristic clinical end points (such as diabetes mellitus, hepatic cirrhosis, and cardiomyopathy) is quite low. There is no test that can predict whether a C282Y homozygote will develop clinical symptoms. The H63D (exon 2, 187C->G) mutation is associated with HH, but the actual clinical effects of this mutation are uncertain. Homozygosity for H63D is insufficient to cause clinically significant iron overload in the absence of additional modifying factors. However, compound heterozygosity for C282Y/H63D has been associated with increased hepatic iron concentrations. Approximately 1% to 2% of individuals with this genotype will develop clinical evidence of iron overload. While individuals with this genotype may have increased iron indices, most will not develop clinical disease without comorbid factors (steatosis, diabetes, or excess alcohol consumption). The clinical significance of a third HFE mutation, S65C (exon 2, 193A->T), appears to be minimal. This rare variant displays a very low penetrance. Compound heterozygosity for C282Y and S65C may confer a low risk for mild HH. Individuals who are heterozygous for S65C and either the wild-type or H63D alleles do not seem to be at an increased risk for HH. The S65C mutation is only reported when it is part of the C282Y/S65C genotype. See Hereditary Hemochromatosis Algorithm in Special Instructions.
Useful For: Establishing or confirming the clinical diagnosis of hereditary hemochromatosis (HH) in adults. HFE genetic testing is NOT recommended for population screening. Testing of individuals with increased transferrin-iron saturation in serum and serum ferritin. With appropriate genetic counseling, predictive testing of individuals who have a family history of HH.

Interpretation: An interpretive report will be provided. For more information about hereditary hemochromatosis testing, see Hereditary Hemochromatosis Algorithm in Special Instructions.

Reference Values: An interpretative report will be provided.


Hemoglobin (Hb) Immunostain, Technical Component Only

Clinical Information: This immunostain uses antibodies to hemoglobin that stain red blood cells and red blood cell precursors in bone marrow and in other sites in a diffuse cytoplasmic staining pattern. This stain may be useful in the diagnosis of erythroleukemia or myelodysplastic neoplasms.

Useful For: Aid in the identification of red blood cells and red blood cell precursors.

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Hemoglobin A1c, Blood

Clinical Information: Diabetes mellitus is a chronic disorder associated with disturbances in carbohydrate, fat, and protein metabolism characterized by hyperglycemia. It is one of the most prevalent diseases, affecting approximately 24 million individuals in the United States. Long-term treatment of the disease emphasizes control of blood glucose levels to prevent the acute complications of ketosis and hyperglycemia. In addition, long-term complications such as retinopathy, neuropathy, nephropathy, and cardiovascular disease can be minimized if blood glucose levels are effectively controlled.
controlled. Hemoglobin A1c (HbA1c) is a result of the nonenzymatic attachment of a hexose molecule to the N-terminal amino acid of the hemoglobin molecule. The attachment of the hexose molecule occurs continually over the entire life span of the erythrocyte and is dependent on blood glucose concentration and the duration of exposure of the erythrocyte to blood glucose. Therefore, the HbA1c level reflects the mean glucose concentration over the previous period (approximately 8-12 weeks, depending on the individual) and provides a much better indication of long-term glycemic control than blood and urinary glucose determinations. Diabetic patients with very high blood concentrations of glucose have from 2 to 3 times more HbA1c than normal individuals. Diagnosis of diabetes includes 1 of the following: - Fasting plasma glucose > or =126 mg/dL - Symptoms of hyperglycemia and random plasma glucose > or =200 mg/dL - Two-hour glucose > or =200 mg/dL during oral glucose tolerance test unless there is unequivocal hyperglycemia, confirmatory testing should be repeated on a different day. The American Diabetes Association (ADA), International Expert Committee (IEC), and the World Health Organization (WHO) recommend the use of HbA1c to diagnose diabetes, using a threshold of 6.5%. The threshold is based upon sensitivity and specificity data from several studies. Advantages to using HbA1c for diagnosis include: - Provides an assessment of chronic hyperglycemia - Assay standardization efforts from the National Glycohemoglobin Standardization Program (NGSP) have been largely successful and the accuracy of HbA1c is closely monitored by manufacturers and laboratories - No fasting is necessary - Intraindividual variability is very low (<2% variation) - A single test could be used for both diagnosing and monitoring diabetes When using HbA1c to diagnose diabetes, an elevated HbA1c should be confirmed with a repeat measurement, except in those individuals who are symptomatic and also have an increased plasma glucose greater than 200 mg/dL. Patients who have an HbA1c between 5.7 and 6.4 are considered at increased risk for developing diabetes in the future. The terms prediabetes, impaired fasting glucose, and impaired glucose tolerance will eventually be phased out by the ADA to eliminate confusion. The ADA recommends measurement of HbA1c (typically 3-4 times per year for type 1 and poorly controlled type 2 diabetic patients, and 2 times per year for well-controlled type 2 diabetic patients) to determine whether a patient's metabolic control has remained continuously within the target range.

**Useful For:** Evaluating the long-term control of blood glucose concentrations in diabetic patients 
Diagnosing diabetes 
Identifying patients at increased risk for diabetes (prediabetes)

**Interpretation:** Diagnosing diabetes American Diabetes Association (ADA) - Hemoglobin A1c (HbA1c) > or =6.5% Therapeutic goals for glycemic control (ADA) - Adults: - Goal of therapy: <7.0% HbA1c - Action suggested: >8.0% HbA1c - Pediatric patients: - Toddlers and preschoolers: <8.5% (but >7.5%) - School age (6-12 years): <8% - Adolescents and young adults (13-19 years): <7.5% The ADA recommendations for clinical practice suggest maintaining a HbA1c value closer to normal yields improved microvascular outcomes for diabetics. Target goals of less than 7% may be beneficial in patients such as those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. However, in patients with significant complications of diabetes, limited life expectancy, or extensive comorbid conditions, targeting a less than 7% goal may not be appropriate. Since the HbA1c assay reflects long-term fluctuations in blood glucose concentration, a diabetic patient who has in recent weeks come under good control may still have a high concentration of HbA1c. The converse is true for a diabetic previously under good control who is now poorly controlled. HbA1c results less than 4.0% are reported with the comment: "Falsely low HbA1c results may be observed in patients with clinical conditions that shorten erythrocyte life span or decrease mean erythrocyte age. HbA1c may not accurately reflect glycemic control when clinical conditions that affect erythrocyte survival are present. Fructosamine may be used as an alternate measurement of glycemic control."

**Reference Values:**
4.0-5.6%

<18 years: Hemoglobin A1c criteria for diagnosing diabetes have not been established for patients who are <18 years of age.
> or =18 years: Increased risk for diabetes (prediabetes): 5.7-6.4% Diabetes: > or =6.5%

Interpretive information based on Diagnosis and Classification of Diabetes Mellitus, American Diabetes Association.

Hemoglobin Electrophoresis Cascade, Blood

Clinical Information: Hemoglobin abnormalities not uncommonly occur as compound disorders (2 or more mutations) that can have complex interactions and variable phenotypes. Although powerful as an adjunct for a complete and accurate diagnosis, genetic methods alone can give incomplete and possibly misleading information due to limitations of the methods. Interpretation of genetic data requires the incorporation of protein analysis results. This profile is well-suited for the classification of hemoglobin disorders. A large number (>1000) of variants of hemoglobin (Hb) have been recognized. They are identified by capital letters (eg, Hb A or Hb S), or by the city in which the variant was first discovered (eg, Hb Koln). Clinical symptoms that can be associated with hemoglobin disorders include microcytosis, sickling disorders, hemolysis, erythrocytosis, cyanosis/hypoxia, long-standing or familial anemia, compensated or episodic anemia, and increased methemoglobin or sulfhemoglobin results.

Mayo Medical Laboratories receives specimens for this test from a wide geographic area and nearly one-half of all specimens received exhibit abnormalities. The most common abnormality is an increase in Hb A2 to about 4% to 8%, which indicates beta-thalassemia minor in the correct clinical context. A wide variety of other hemoglobinopathies also have been encountered. Ranked in order of relative frequency, these are: Hb S (sickle cell disease and trait), C, E, Lepore, G-Philadelphia, H, D-Los Angeles, Koln, Constant Spring, O-Arab, and others. Hb C and S are found mostly in people from west or central Africa and Hb E and H in people from Southeast Asia. Hemoglobin electrophoresis is often used in the evaluation of unexplained microcytosis, thus accounting for the frequent detection of Hb Lepore, which is relatively common in Italians and others of Mediterranean ancestry and in Hb E, which is relatively common in Southeast Asians resettled in the United States; microcytosis is characteristic of both Hb Lepore and Hb E. Alpha-thalassemia is very common in the United States, occurring in approximately 30% of African Americans and accounting for the frequent occurrence of microcytosis in persons of this ethnic group. Some alpha-thalassemias (ie, hemoglobin variants H, Barts, and Constant Spring) are easily identified in the hemoglobin electrophoresis protocol. However, alpha-thalassemias that are from only 1 or 2 alpha-globin gene deletions are not recognized by protein studies alone. For the diagnosis of alpha-thalassemias, deletion and duplication testing is required.

Useful For: Diagnosis and comprehensive classification of thalassemias and hemoglobin variants

Interpretation: The types of hemoglobin present are identified, quantitated, and an interpretive report is issued.

Reference Values:

HEMOGLOBIN A
1-30 days: 5.9-77.2%
1-2 months: 7.9-92.4%
3-5 months: 54.7-97.1%
6-8 months: 80.0-98.0%
9-12 months: 86.2-98.0%
13-17 months: 88.8-98.0%
18-23 months: 90.4-98.0%
> or =24 months: 95.8-98.0%

HEMOGLOBIN A2
1-30 days: 0.0-2.1%
**HEMOGLOBIN F**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-30 days</td>
<td>22.8-92.0%</td>
</tr>
<tr>
<td>1-2 months</td>
<td>7.6-89.8%</td>
</tr>
<tr>
<td>3-5 months</td>
<td>1.6-42.2%</td>
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<tr>
<td>6-8 months</td>
<td>0.0-16.7%</td>
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<tr>
<td>9-12 months</td>
<td>0.0-10.5%</td>
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<tr>
<td>13-17 months</td>
<td>0.0-7.9%</td>
</tr>
<tr>
<td>18-23 months</td>
<td>0.0-6.3%</td>
</tr>
<tr>
<td>&gt; or =24 months</td>
<td>0.0-0.9%</td>
</tr>
</tbody>
</table>

**VARIANT**

No abnormal variants

**VARIANT 2**

No abnormal variants

**VARIANT 3**

No abnormal variants


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**Hemoglobin F, Red Cell Distribution, Blood**

**Clinical Information:** More than 75% of the hemoglobin of the newborn is hemoglobin F (Hb F); it diminishes over a period of several months to adult levels, reducing to less than 2% by age 1 and less than 1% by age 2. Hb F may constitute 90% of the total hemoglobin in patients with beta-thalassemia major or other combinations of beta thalassemia and fetal hemoglobin (HPFH) mutations. Hb F is often mildly to moderately elevated in sickle cell disease, aplastic anemia, acute leukemia, and myeloproliferative disorders such as juvenile myelomonocytic leukemia (JMML), hereditary spherocytosis, and alpha-thalassemia minor. It is commonly increased in hemoglobinopathies associated with hemolysis. Hb F increases to as high as 10% during normal pregnancy. Hb F is also increased due to medications such as hydroxyurea, decitabine, and lenalidomide. Elevation in Hb F has a been cited as a discriminator between Diamond-Blackfan congenital pure red cell aplasia (elevated) and transient erythroblastopenia of childhood (normal), but whether this simply reflects the chronicity of anemia inherent to the former condition rather than a specific finding is unclear. In the common (large deletional) form of the genetic trait hereditary persistence of HPFH, all of the erythrocytes contain Hb F. When tested by flow cytometry using specificity for Hb F, these HPFH cases display a homocellular distribution pattern of Hb F within the red cell population. Other causes of increased Hb F including delta beta thalassemia, hydroxyurea, and some nondeletional HPFH mutations typically display a heterocellular distribution of Hb F within the red cells, reflecting disparate populations of F cells and cells lacking Hb F. Quantification of Hb F percentage should be determined prior to flow cytometry of Hb F red cell distribution to establish the appropriateness of this test. The flow cytometry analysis of elevated Hb F levels is useful when Hb F percentage is between 15% to 35% and the clinical differential diagnosis includes large deletional HPFH. Hb F percentages below 15% are likely not due to large deletional HPFH and causes of Hb F percentages above 35% are better confirmed by molecular and family studies.

**Useful For:** Distinguishing large deletional hereditary persistence of fetal hemoglobin from other conditions with increased percentage of fetal hemoglobin Determining the distribution of Hb F within red blood cells

**Interpretation:** Homocellular distribution of fetal hemoglobin is found in large deletional hereditary
persistence of fetal hemoglobin. Heterocellular distribution is found in delta beta thalassemia, medication induced, and other causes of increased hemoglobin F.

**Reference Values:**
Only orderable as a reflex. For more information see:
- HAEVP / Hemolytic Anemia Evaluation
- HBELC / Hemoglobin Electrophoresis Cascade, Blood
- MEVP / Methemoglobinemia Evaluation
- REVE / Erythrocytosis Evaluation
- THEVP / Thalassemia and Hemoglobinopathy Evaluation

Reported as heterocellular or homocellular

**Clinical References:**
levels are needed to guide further therapy.

**Useful For:** Monitoring patients with sickling disorders who have received hydroxyurea or transfusion therapy

**Interpretation:** Clinically, optimal levels of hemoglobin S (Hb S) and hemoglobin F (Hb F) are patient specific and depend on a number of factors including response to therapy. This test will be performed by capillary electrophoresis and any variant present will be reported as their zone only, including Hb S. No confirmatory functional study such as sickle solubility will be performed. Information reported: Percentages of hemoglobin A (Hb A), hemoglobin A2 (Hb A2), Hb F and any variant present. Variants will be reported as zones and are not specific, even if present in Z5 (Zone S). If the identity of the variant has not been previously confirmed, diagnostic hemoglobin electrophoresis is necessary (see HBELC / Hemoglobin Electrophoresis Cascade, Blood).

**Reference Values:**

**HEMOGLOBIN A**
1-30 days: 5.9-77.2%
1-2 months: 7.9-92.4%
3-5 months: 54.7-97.1%
6-8 months: 80.0-98.0%
9-12 months: 86.2-98.0%
13-17 months: 88.8-98.0%
18-23 months: 90.4-98.0%
> or =24 months: 95.8-98.0%

**HEMOGLOBIN A2**
1-30 days: 0.0-2.1%
1-2 months: 0.0-2.6%
3-5 months: 1.3-3.1%
> or =6 months: 2.0-3.3%

**HEMOGLOBIN F**
1-30 days: 22.8-92.0%
1-2 months: 7.6-89.8%
3-5 months: 1.6-42.2%
6-8 months: 0.0-16.7%
9-12 months: 0.0-10.5%
13-17 months: 0.0-7.9%
18-23 months: 0.0-6.3%
> or =24 months: 0.0-0.9%

**VARIANT 1**
0.0

**VARIANT 2**
0.0

**VARIANT 3**
0.0

**Clinical References:**

Hemoglobin, Blood

Clinical Information: Hemoglobin transports oxygen and CO2. This activity is decreased in anemia and increased in polycythemia, erythrocytosis, and dehydration. Hemoglobin measurements are used as clinical guides in the diagnosis or monitoring of many diseases.

Useful For: Screening tool to confirm a hematologic disorder Establishing or ruling out a diagnosis Detecting an unsuspected hematologic disorder Monitoring the effects of radiation or chemotherapy

Interpretation: Results outside of normal value ranges may reflect a primary disorder of the cell-producing organs or an underlying disease. Results should be interpreted in conjunction with the patient's clinical picture and appropriate additional testing performed.

Reference Values:

<table>
<thead>
<tr>
<th>HEMOGLOBIN</th>
<th>Males:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14 days:</td>
<td>13.9-19.1 g/dL</td>
</tr>
<tr>
<td>15 days-4 weeks:</td>
<td>10.0-15.3 g/dL</td>
</tr>
<tr>
<td>5 weeks-7 weeks:</td>
<td>8.9-12.7 g/dL</td>
</tr>
<tr>
<td>8 weeks-5 months:</td>
<td>9.6-12.4 g/dL</td>
</tr>
<tr>
<td>6 months-23 months:</td>
<td>10.1-12.5 g/dL</td>
</tr>
<tr>
<td>24 months-35 months:</td>
<td>10.2-12.7 g/dL</td>
</tr>
<tr>
<td>3-5 years:</td>
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<tr>
<td>6-8 years:</td>
<td>11.5-14.3 g/dL</td>
</tr>
<tr>
<td>9-10 years:</td>
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<td>11-14 years:</td>
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<tr>
<td>15-17 years:</td>
<td>13.3-16.9 g/dL</td>
</tr>
<tr>
<td>Adults:</td>
<td>13.2-16.6 g/dL</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Females:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14 days:</td>
<td>13.4-20.0 g/dL</td>
</tr>
<tr>
<td>15 days-4 weeks:</td>
<td>10.8-14.6 g/dL</td>
</tr>
<tr>
<td>5 weeks-7 weeks:</td>
<td>9.2-11.4 g/dL</td>
</tr>
<tr>
<td>8 weeks-5 months:</td>
<td>9.9-12.4 g/dL</td>
</tr>
<tr>
<td>6 months-35 months:</td>
<td>10.2-12.7 g/dL</td>
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<td>3-5 years:</td>
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<td>6-8 years:</td>
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<td>9-10 years:</td>
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<tr>
<td>11-17 years:</td>
<td>11.9-14.8 g/dL</td>
</tr>
<tr>
<td>Adults:</td>
<td>11.6-15.0 g/dL</td>
</tr>
</tbody>
</table>

**Hemoglobin, Qualitative, Urine**

**Clinical Information:** Free hemoglobin (Hgb) in urine usually is the result of lysis of RBCs present in the urine due to bleeding into the urinary tract (kidney, ureters, bladder). Less commonly, intravascular hemolysis (eg, transfusion reaction, hemolytic anemia, paroxysmal hemoglobinuria) may result in excretion of free Hgb from blood into urine. Injury to skeletal or cardiac muscle results in the release of myoglobin, which also is detected by this assay. Conditions associated with myoglobinuria include hereditary myoglobinuria, phosphorylase deficiency, sporadic myoglobinuria, exertional myoglobinuria in untrained individuals, crush syndrome, myocardial infarction, myoglobinuria of progressive muscle disease, and heat injury.

**Useful For:** Screening for hematuria, myoglobinuria, or intravascular hemolysis

**Interpretation:** Free hemoglobin (Hgb), in the presence of RBCs, indicates bleeding into the urinary tract. Free Hgb, in the absence of RBCs, is consistent with intravascular hemolysis. Note: RBCs may be missed if lysis occurred prior to analysis; the absence of RBCs should be confirmed by examining a fresh specimen. The test is equally sensitive to hemoglobin and to myoglobin. The presence of myoglobin may be confirmed by MYOU / Myoglobin, Urine.

**Reference Values:**
- Appearance (internal specimens only): normal
- Hemoglobin: negative
- RBCs (internal specimens only): 0-2 rbc/s/hpf

**Clinical References:** Fairbanks, V.F. and Klee G.G., Textbook of Clinical Chemistry 1986, Chapter 15, p 1562

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**Hemolytic Anemia Evaluation**

**Clinical Information:** Hemolytic anemia (HA) is characterized by increased red cell destruction and a decreased red cell life span. Patients usually have decreased hemoglobin concentration, hematocrit, and red blood cell count, but some can have compensated disorders, and symptoms such as reticulocytosis, pigmented gallstones, and decreased haptoglobin are factors that raise clinical suspicion. Blood smear abnormalities may include spherocytes, schistocytes, stomatocytes, polychromasia, basophilic stippling, and target cells. Osmotic fragility can be increased due to the presence of spherocytes. These are all nonspecific features that can be present in both hereditary and acquired hemolytic disorders. Inherited hemolytic disorders may include red cell membrane disorders, red cell enzyme defects, or abnormalities in the hemoglobin molecule in the red cell. This panel assesses for possible causes of congenital/hereditary causes of hemolytic anemia and does not evaluate for acquired causes. Therefore, the anemia should be lifelong or familial in nature. Examples of acquired HA (which should be excluded prior to ordering this panel) include: autoimmune HA (direct Coombs-positive HA, Coombs-negative autoimmune HA), cold agglutinin disease, paroxysmal nocturnal hemoglobinuria, paroxysmal cold hemoglobinuria, mechanical hemolysis (aortic stenosis or prosthetic heart valves), disseminated intravascular coagulation/thrombotic microangiopathy, and drug-induced HA. This consultation evaluates for a hereditary cause of increased red cell destruction and includes testing for red cell membrane disorders, such as hereditary spherocytosis and hereditary pyropoikilocytosis, hemoglobinopathies, and red cell enzyme abnormalities. This panel is of limited use in patients with a history of recent transfusion and should be ordered as remote a date from transfusion as possible in those patients who are chronically transfused.

**Useful For:** Evaluation of lifelong or inherited hemolytic anemias, including red cell membrane disorders, unstable or abnormal hemoglobin variants, and red cell enzyme disorders This evaluation is not suitable for acquired causes of hemolysis.

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Definitive results and an interpretive report will be provided.
Hemophilia A F8 Gene, Intron 1 and 22 Inversion Mutation Analysis, Amniotic Fluid or Chorionic Villus Sampling

Clinical Information: Hemophilia A (HA) is due to a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males. Males are typically affected with bleeding symptoms, whereas carrier females generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of carrier females have FVIII activity levels below 35% and are at risk for bleeding. Bleeding, the most common clinical symptom in individuals with HA, correlates with FVIII activity levels. FVIII activity levels of <1% are associated with severe disease, 1% to 5% activity with moderate disease, and 5% to 40% with mild disease. In males with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA, bleeding may occur only after surgery or trauma. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have a mutation in F8 (ie, intron 1 and 22 inversions, point mutations, insertions, and deletions). The intron 1 and 22 inversion mutations account for approximately 50% of mutations associated with severe HA. These inversions are typically not identified in patients with mild or moderate HA. It is recommended that the F8 mutation be confirmed in the affected male or obligate carrier female prior to testing at-risk individuals. Affected males are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate carrier females are identified by family history assessment. If the intron inversion assays do not detect an inversion in these individuals, additional analysis (ie, F8 sequencing) may be able to identify the familial mutation. Of note, not all females with an affected son are germline carriers of a F8 mutation, as de novo mutations in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 mutation. Importantly, there is a small risk for recurrence even when the familial F8 mutation is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

Useful For: Prenatal testing for hemophilia A when a mutation has not been identified in the family.

Interpretation: An interpretive report will be provided.

Reference Values: Not applicable

Hemophilia A F8 Gene, Intron 1 and 22 Inversion Mutation Analysis, Whole Blood

Clinical Information: Hemophilia A (HA) is caused by a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males. Males are typically affected with bleeding symptoms, whereas carrier females generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of carrier females have FVIII activity levels below 35% and are at risk for bleeding. Bleeding, the most common clinical symptom in individuals with HA, correlates with FVIII activity levels. FVIII activity levels of <1% are associated with severe disease, 1% to 5% activity with moderate disease, and 5% to 40% with mild disease. In males with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA, bleeding may occur only after surgery or trauma. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have a mutation in F8 (ie, intron 1 and 22 inversions, point mutations, insertions, and deletions). The intron 1 and 22 inversion mutations account for approximately 50% of mutations associated with severe HA. These inversions are typically not identified in patients with mild or moderate HA. It is recommended that the F8 mutation be confirmed in the affected male or obligate carrier female prior to testing at-risk individuals. Affected males are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate carrier females are identified by family history assessment. If the intron inversion assays do not detect an inversion in these individuals, additional analysis (ie, F8 sequencing) may be able to identify the familial mutation. Of note, not all females with an affected son are germline carriers of a F8 mutation, as de novo mutations in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 mutation. Importantly, there is a small risk for recurrence even when the familial F8 mutation is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

Useful For: First-tier molecular testing for males affected with severe hemophilia A when a mutation has not been identified in the family. Determining hemophilia A carrier status for at-risk females, ie, individuals with a family history of severe hemophilia A

Interpretation: An interpretive report will be provided.

Reference Values: Not applicable


Hemophilia A F8 Gene, Intron 1 Inversion Known Mutation Analysis, Amniotic Fluid or Chorionic Villus Sampling

Clinical Information: Hemophilia A (HA) is caused by a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males. Males are typically affected with bleeding symptoms, whereas carrier females generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of carrier females have FVIII activity levels below 35% and are at risk for bleeding. Bleeding is the most common clinical
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**Useful For:** Prenatal testing for hemophilia A when a F8 intron 1 inversion has been identified in a family member.

**Interpretation:** An interpretive report will be provided.

**Reference Values:** Not applicable

**Clinical References:**

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**F81B 60555 Hemophilia A F8 Gene, Intron 1 Inversion Known Mutation, Whole Blood**

**Clinical Information:** Hemophilia A (HA) is caused by a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males. Males are typically affected with bleeding symptoms, whereas carrier females generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of carrier females have FVIII activity levels below 35% and are at risk for bleeding. Bleeding, the most common clinical symptom in individuals with HA, correlates with FVIII activity levels. FVIII activity levels of <1% are associated with severe disease, 1% to 5% activity with moderate disease, and 5% to 40% with mild disease. In males with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA, bleeding may occur only after surgery or trauma. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have a mutation in F8 (ie, intron 1 and 22 inversions, point mutations, insertions, and deletions). The intron 1 inversion mutation accounts for approximately 5% of mutations associated with severe HA. These inversions are typically not identified in patients with mild or moderate HA. Intron 1 inversion known mutation analysis is only recommended for individuals when an intron 1 inversion has already been identified in the family. If a familial mutation has not been identified in a severely affected HA patient the F8 gene intron 1 and 22 inversion analysis (F8INV / Hemophilia A F8 Gene, Intron 1 and 22 Inversion Mutation Analysis, Whole Blood) should be ordered. If the intron 1 inversion analysis is negative, the tested individual has not inherited the familial mutation. It is recommended that the F8 mutation be confirmed in the affected male or obligate carrier female prior to testing at-risk individuals. Affected males are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while
obligate carrier females are identified by family history assessment. If the intron inversion assays do not detect an inversion in these individuals, additional analysis (ie, F8 sequencing) may be able to identify the familial mutation. Of note, not all females with an affected son are germline carriers of a F8 mutation, as de novo mutations in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 mutation. Importantly, there is a small risk for recurrence even when the familial F8 mutation is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

**Useful For:** First-tier molecular testing for males affected with severe hemophilia A, when a familial intron 1 inversion has been previously identified. Determining hemophilia A carrier status for at-risk females, ie, individuals with a family history of severe hemophilia A due to F8 intron 1 inversion

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Not applicable

**Clinical References:**

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**Hemophilia A F8 Gene, Intron 22 Inversion Known Mutation, Whole Blood**

**Clinical Information:** Hemophilia A (HA) is caused by a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males. Males are typically affected with bleeding symptoms, whereas carrier females generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of carrier females have FVIII activity levels below 35% and are at risk for bleeding. Bleeding, the most common clinical symptom in individuals with HA, correlates with FVIII activity levels. FVIII activity levels of <1% are associated with severe disease, 1% to 5% activity with moderate disease, and 5% to 40% with mild disease. In males with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA, bleeding may occur only after surgery or trauma. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have a mutation in F8 (ie, intron 1 and 22 inversions, point mutations, insertions, and deletions). The intron 22 inversion mutations account for approximately 45% of mutations associated with severe HA. These inversions are typically not identified in patients with mild or moderate HA. Intron 22 inversion known mutation analysis is only recommended for individuals when an intron 22 inversion has already been identified in the family. If a familial mutation has not been identified in a severely affected HA patient the F8 gene intron 1 and 22 inversion analysis (F8INV / Hemophilia A F8 Gene, Intron 1 and 22 Inversion Mutation Analysis, Whole Blood) should be ordered. If the intron 22 inversion analysis is negative, the tested individual has not inherited the familial mutation. It is recommended that the F8 mutation be confirmed in the affected male or obligate carrier female prior to testing at-risk individuals. Affected males are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate carrier females are identified by family history assessment. If the intron inversion assays do not detect an inversion in these individuals, additional analysis (ie, F8 sequencing) may be able to identify the familial mutation. Of note, not all females with an affected son are germline carriers of a F8 mutation, as de novo mutations in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 mutation. Importantly, there is a small risk for recurrence even when the familial F8 mutation is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

**Useful For:** First-tier molecular testing for males affected with severe hemophilia A, when a familial intron 22 inversion has been previously identified. Determining hemophilia A carrier status for at-risk females, ie, individuals with a family history of severe hemophilia A due to F8 intron 22 inversion
**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Not applicable

**Clinical References:**

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**Hemophilia A F8 Gene, Intron 22 Inversion Mutation Analysis, Amniotic Fluid or Chorionic Villus Sampling**

**Clinical Information:**
Hemophilia A (HA) is caused by a deficiency of clotting factor VIII (FVIII). HA is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males. Males are typically affected with bleeding symptoms, whereas carrier females generally do not have bleeding symptoms but are at risk of having affected sons. Rarely, approximately 10% of carrier females have FVIII activity levels below 35% and are at risk for bleeding. Bleeding, the most common clinical symptom in individuals with HA, correlates with FVIII activity levels. FVIII activity levels of <1% are associated with severe disease, 1% to 5% activity with moderate disease, and 5% to 40% with mild disease. In males with severe deficiency, spontaneous bleeding may occur. In individuals with mild HA, bleeding may occur only after surgery or trauma. FVIII is encoded by the factor VIII (F8) gene. Approximately 98% of patients with a diagnosis of HA are found to have a mutation in F8 (ie, intron 1 and 22 inversions, point mutations, insertions, and deletions). The intron 22 inversion mutations account for approximately 45% of mutations associated with severe HA. These inversions are typically not identified in patients with mild or moderate HA. Intron 22 inversion known mutation analysis on a prenatal specimen can only be performed when there is a known intron 22 inversion in the family. It is recommended that the F8 mutation be confirmed in the affected male or obligate carrier female prior to testing at-risk individuals. Affected males are identified by FVIII activity (F8A / Coagulation Factor VIII Activity Assay, Plasma) and clinical evaluation, while obligate carrier females are identified by family history assessment. Of note, not all females with an affected son are germline carriers of a F8 mutation, as de novo mutations in F8 do occur. Approximately 20% of mothers of isolated cases do not have an identifiable germline F8 mutation. Importantly, there is a small risk for recurrence even when the familial F8 mutation is not identified in the mother of the affected patient due to the possibility of germline mosaicism.

**Useful For:** Prenatal testing for hemophilia A when a F8 intron 22 inversion has been identified in a family member.

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Not applicable

**Clinical References:**
Hemophilia B, F9 Gene Known Mutation Analysis, Amniotic Fluid or Chorionic Villus Sampling

Clinical Information: Hemophilia B, factor IX deficiency, is an X-linked recessive bleeding disorder with an incidence of about 1 per 30,000 live male births. It occurs as a result of mutations in the factor IX (F9) gene. As many as one-third of hemophiliacs have no affected family members, which reflects a high mutation rate in the F9 gene (ie, de novo mutations). Hemophilia B affects males; however, all male offspring from an affected male will be normal. Although all female offspring of affected males will be obligatory carriers, they rarely have symptomatic bleeding. In contrast, female offspring of female carriers of hemophilia B have a 50% chance of being carriers themselves, and each male offspring has a 50% chance of being affected. Based on factor IX activity, hemophilia B is classified as severe (factor IX activity <1%), moderate (factor IX activity 1%-5%), or mild (factor IX activity >5%-40%). In males, a low factor IX activity level establishes the diagnosis of hemophilia B. However, the wide range of normal factor IX activity precludes an accurate assessment of carrier status in females, thus making molecular testing essential in assessment of carrier status. Inhibitors to factor IX activity are estimated to occur in 5% to 8% of hemophilia B patients, much less than that of hemophilia A. Inhibitor risk correlates with genotype and typically occurs in patients with either partial or total deletions of the F9 gene or in certain nonsense mutations that result in no circulating factor IX:antigen. More recently, it has been observed that a subset of patients with such mutations may be at risk of experiencing anaphylactic reactions to the factor IX replacement therapy.

Useful For: Prenatal testing for a known familial pathogenic mutation in the F9 gene in a fetus who is at risk for inheriting this mutation

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be issued that will include specimen information, assay information, background information, and conclusions based on the test results (ie, information about the mutation).


Hemophilia B, F9 Gene Known Mutation, Whole Blood

Clinical Information: Hemophilia B, factor IX deficiency, is an X-linked recessive bleeding disorder with an incidence of about 1 per 30,000 live male births. It occurs as a result of mutations in the factor IX (F9) gene. As many as one-third of hemophiliacs have no affected family members, which reflects a high mutation rate in the F9 gene (ie, de novo mutations). Hemophilia B affects males; however, all male offspring from an affected male will be normal. Although all female offspring of affected males will be obligatory carriers, they rarely have symptomatic bleeding. In contrast, female offspring of female carriers of hemophilia B have a 50% chance of being carriers themselves, and each male offspring has a 50% chance of being affected. Based on factor IX activity, hemophilia B is classified as severe (factor IX activity <1%), moderate (factor IX activity 1%-5%), or mild (factor IX activity >5%-40%). In males, a low factor IX activity level establishes the diagnosis of hemophilia B. However, the wide range of normal factor IX activity precludes an accurate assessment of carrier status in females, thus making molecular testing essential in assessment of carrier status. Inhibitors to factor IX activity are estimated to occur in 5% to 8% of patients, much less than that of hemophilia A. Inhibitor risk correlates with genotype and typically occurs in patients with either partial or total deletions of the F9 gene or in certain nonsense mutations that result in no circulating factor IX antigen. More recently, it has been observed that a subset of patients with such mutations may be at risk of experiencing anaphylactic reactions to the factor IX replacement therapy.

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Useful For: Diagnostic, targeted testing for hemophilia B when a mutation has been identified in a family member. Carrier testing of females in whom the familial F9 genotype is known.

Interpretation: An interpretive report will be provided.

Reference Values: Not applicable.

Clinical References:

Hemophilia B, F9 Gene Mutation Analysis, Amniotic Fluid or Chorionic Villus Sampling

Clinical Information: Hemophilia B, factor IX deficiency, is an X-linked recessive bleeding disorder with an incidence of about 1 per 30,000 live male births. It occurs as a result of mutations in the factor IX (F9) gene. As many as one-third of hemophiliacs have no affected family members, which reflects a high mutation rate in the F9 gene (ie, de novo mutations). Hemophilia B affects males; however, all male offspring from an affected male will be normal. Although all female offspring of affected males will be obligatory carriers, they rarely have symptomatic bleeding. In contrast, female offspring of female carriers of hemophilia B have a 50% chance of being carriers themselves and each male offspring has a 50% chance of being affected. Based on factor IX activity, hemophilia B is classified as severe (factor IX activity <1%), moderate (factor IX activity 1%-5%), or mild (factor IX activity >5%-40%). In males, a low factor IX activity level establishes the diagnosis of hemophilia B. However, the wide range of normal factor IX activity precludes an accurate assessment of carrier status in females, thus making molecular testing essential in assessment of carrier status. Inhibitors to factor IX activity are estimated to occur in 5% to 8% of patients, much less than that of hemophilia A. Inhibitor risk correlates with genotype and typically occurs in patients with either partial or total deletions of the F9 gene or in certain nonsense mutations that result in no circulating factor IX:antigen. More recently, it has been observed that a subset of patients with such mutations may be at risk of experiencing anaphylactic reactions to the factor IX replacement therapy.

Useful For: Prenatal testing for a pathogenic mutation in the F9 gene in a fetus with a strong, confirmed family history of congenital hemophilia B (factor IX activity deficiency) in the exceptional circumstance where a familial mutation cannot be otherwise ascertained.

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be issued that will include specimen information, assay information, background information, and conclusions based on the test results (ie, information about the mutation and carrier status).

Clinical References:

Hemophilia B, F9 Gene Mutation Analysis, Whole Blood

Clinical Information: Hemophilia B, factor IX deficiency, is an X-linked recessive bleeding disorder.
disorder with an incidence of about 1 per 30,000 live male births. It occurs as a result of mutations in the factor IX (F9) gene. As many as one-third of hemophiliacs have no affected family members, which reflects a high mutation rate in the F9 gene (ie, de novo mutations). Hemophilia B affects males. However, all male offspring from an affected male will be normal. Although all female offspring of affected males will be obligatory carriers, they rarely have symptomatic bleeding. In contrast, female offspring of female carriers of hemophilia B have a 50% chance of being carriers themselves and each male offspring has a 50% chance of being affected. Based on factor IX activity, hemophilia B is classified as severe (factor IX activity <1%), moderate (factor IX activity 1%-5%), or mild (factor IX activity >5%-40%). In males, a low factor IX activity level establishes the diagnosis of hemophilia B. However, the wide range of normal factor IX activity precludes an accurate assessment of carrier status in females, thus making molecular testing essential in assessment of carrier status. Inhibitors to factor IX activity are estimated to occur in 5% to 8% of hemophilia patients, much less than that of hemophilia A. Inhibitor risk correlates with genotype and typically occurs in patients with either partial or total deletions of the F9 gene or in certain nonsense mutations that result in no circulating factor IX antigen. More recently, it has been observed that a subset of patients with such mutations may be at risk of experiencing anaphylactic reactions to the factor IX replacement therapy.

**Useful For:** Ascertaining the causative mutation in the F9 gene of patients with congenital hemophilia B (factor IX activity deficiency) Carrier testing of females in whom the familial F9 genotype is unknown

**Interpretation:** An interpretive report will be issued which will include specimen information, assay information, background information, and conclusions based on the test results (ie, information about the mutation and carrier status).

**Reference Values:**

Not applicable

**Clinical References:**


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**HemoQuant, Feces**

**Clinical Information:** Several noninvasive tests are available to detect gastrointestinal (GI) bleeding. However, guaiac type and immunochemical tests for occult bleeding are affected by the presence of reducing or oxidizing substances and are insensitive for the detection of proximal gut bleeding, where most clinically significant occult GI bleeding occurs. The HemoQuant test is the most reliable, noninvasive test currently available for detecting bleeding of the esophago-GI tract. Unlike other tests for blood in feces, this test detects both intact heme and porphyrins from partly degraded heme. Additionally, test results are not complicated by either the water content of the specimen or the presence of reducing or oxidizing substances. Furthermore, HemoQuant testing is sensitive to both proximal and distal sources of occult GI bleeding.

**Useful For:** Detection of blood in feces HemoQuant is the most appropriate fecal occult blood test to use in the evaluation of iron deficiency Other useful applications include the detection of bleeding as a complication of anticoagulant therapy and other medication regimens

**Interpretation:** Elevated levels are an indicator of the presence of blood in the feces, either from benign or malignant causes. This test is not specific for bowel cancer.

**Reference Values:**

Normal:

< 2.0 mg total hemoglobin/g feces

Marginal:

2.0-3.0 mg total hemoglobin/g feces

2.0-4.0 mg total hemoglobin/g feces*
Elevated:
>3.0 mg total hemoglobin/g feces
>4.0 mg total hemoglobin/g feces*

*Alternative reference values for persons who have ingested red meat or aspirin during any of the 3 days preceding specimen collection.

**Clinical References:**

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**Hemosiderin, Urine**

**Clinical Information:** When the plasma hemoglobin level is >50 to 200 mg/dL after hemolysis, the capacity of haptoglobin to bind hemoglobin is exceeded, and hemoglobin readily passes through the glomeruli of the kidney. Part of the hemoglobin is absorbed by the proximal tubular cells where the hemoglobin iron is converted to hemosiderin. When these tubular cells are later shed into the urine, hemosiderinuria results. If all of the hemoglobin cannot be absorbed into the tubular cells, hemoglobinuria results. Hemosiderin is found as yellow-brown granules that are free or in epithelial cells and occasionally in casts in an acidic or neutral urine.

**Useful For:** Detecting hemosiderinuria, secondary to excess hemolysis, as in incompatible blood transfusions, severe acute hemolytic anemia, or hemochromatosis

**Interpretation:** A positive hemosiderin indicates excess red cell destruction. Hemosiderinuria may still be detected after hemoglobin has cleared from the urine and hemoglobin dipstick is negative.

**Reference Values:**
- Hemosiderin: negative (reported as positive or negative)
- Hemoglobin (internal specimens only): negative
- RBC (internal specimens only): 0-2 rbc/hpf


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**Hemp Western Water (Acnida tamariscina) IgE**

**Interpretation:**
- Class IgE (kU/L) Comment
  - 0 <0.35 Below Detection
  - 1 0.35 – 0.69 Low Positive
  - 2 0.70 – 3.49 Moderate Positive
  - 3 3.50 – 17.49 Positive
  - 4 17.50 – 49.99 Strong Positive
  - 5 50.00 – 99.99 Very Strong Positive
  - 6 >99.99 Very Strong Positive

**Reference Values:**
- <0.35 kU/L

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**Heparin Anti-Xa, Plasma**

**Clinical Information:** Heparins are sulphated glycosaminoglycans that inactivate thrombin, factor Xa, and several other coagulation factors; act by enhancing activity of the plasma coagulation inhibitor, antithrombin III (AT III); and prolong the activated partial thromboplastin time (APTT). The anti-Xa assay is the preferred method for monitoring low-molecular-weight heparin (LMWH) therapy because of reduced sensitivity of APTT. Heparin is absent in normal plasma. The heparin level obtained has to be analyzed taking into account the treatment given to the patient (type of heparin, dosage, administration mode, time of sampling, etc) and the desired therapeutic effect. It is clinically
recommended that platelet counts be monitored frequently in patients receiving unfractionated heparin (UFH) or LMWH in order to detect heparin-induced thrombocytopenia (HIT).

**Useful For:** Measuring heparin concentration: -In patients treated with low-molecular-weight heparin preparations - In the presence of prolonged baseline activated partial thromboplastin time (APTT) (eg, lupus anticoagulant, "contact factor" deficiency, etc) -When unfractionated heparin dose needed to achieve desired APTT prolongation is unexpectedly higher (>50%) than expected Not useful for monitoring therapy with the heparinoid "danaparoid"

**Interpretation:** Results above the therapeutic range may be supratherapeutic suggesting that the heparin dose may need to be decreased. Results below the therapeutic range may be subtherapeutic suggesting that the heparin dose may need to be increased.

**Reference Values:**
Adult Therapeutic Range
UFH therapeutic range: 0.30-0.70 IU/mL
(6 hours following initiation or dose adjustment)
LMWH therapeutic range: 0.50-1.00 IU/mL for twice daily dosing*
LMWH therapeutic range: 1.00-2.00 IU/mL for once daily dosing*
LMWH prophylactic range: 0.10-0.30 IU/mL
(*sample obtained 4-6 hours following subcutaneous injection)

Heparin Anti-Xa assay is used to measure heparin concentrations in patients receiving low-molecular-weight heparin or unfractionated heparin.

**Clinical References:**

**Heparin Cofactor II**

**Reference Values:**
65 - 145%

**Heparin-PF4 IgG Antibody (HIT), Serum**

**Clinical Information:** Thrombocytopenia in patients treated with heparin is relatively common and has diverse, sometimes multifactorial, causes. Among the possible causes of thrombocytopenia in such patients, immune-mediated heparin-dependent thrombocytopenia (HIT) is clinically important because of its frequency and its associated risk of paradoxical new or progressive thrombosis. HIT, also called heparin-associated thrombocytopenia (HAT), consists of 2 distinct clinicopathologic syndromes. The first, sometimes designated type I HIT (HIT-I) or nonimmune HAT, is a common benign condition that is not immunologically mediated. Type I HIT is characterized by a mild decrease of the platelet count (typically < or =30% decrease from baseline) occurring early (days) in the course of treatment with heparin, especially intravenous unfractionated heparin (UFH), and which does not progress and may resolve despite continuation of heparin therapy. The second, more serious immune-mediated syndrome, sometimes designated type II heparin-induced thrombocytopenia (HIT-II), occurs in up to 1% to 5% of patients treated with UFH. It is typically characterized by onset of thrombocytopenia between days 5 and 10 of UFH therapy, but thrombocytopenia can arise earlier or later in association with continued heparin
negative H/PF4 antibody ELISA result, a negative H/PF4 antibody ELISA result does not exclude the
Because up to 10% of patients with clinical heparin-induced thrombocytopenia (HIT) may have a
negative predictive value for exclusion of clinical type II heparin-induced thrombocytopenia (HIT-II).
Equivocal A negative result of testing for human platelet factor 4 (H/PF4) antibodies has about a 90%
Range <0.400 Not done Negative Positive > or =0.400 > or =50% Positive Equivocal > or =0.400 <50%
accompany test reports, when indicated. HIT ELISA OD Heparin Inhibition Interpretation Normal
results and interpretations are depicted in the following table. Interpretive comments will also
Interpretation:
Useful For: Detection of IgG antibodies directed against heparin/platelet factor 4 complexes that are
implicated in the pathogenesis of immune-mediated type II heparin-induced thrombocytopenia (HIT-II).
Clinical picture of HIT type II: -In patients not previously exposed to heparin -Decrease in platelet
count (thrombocytopenia) of 50% or more from baseline or postoperative peak -Onset of
thrombocytopenia beginning approximately 5 to 10 days after initiation of heparin this may or may not
be associated with new or progressive thrombosis in patients treated with heparin Patients previously
exposed to heparin (especially within the preceding 100 days), in addition to the above findings, the
onset of thrombocytopenia could occur within 24 to 48 hours after reexposure to heparin
Results are reported as: 1) Heparin-induced thrombocytopenia (HIT) enzyme-linked
imunosorbent assay (ELISA) OD; 2) Heparin inhibition (%); 3) Interpretation. Typical patterns of
and among other etiologies of thrombocytopenia occurring in patients receiving heparin. However, the
development of new or progressive thrombosis is one defining clinical feature of HIT-II. Recent studies
provide evidence that HIT-II is caused, in at least 90% of cases, by antibodies to antigen complexes of
heparinoid (heparin or similar glycosaminoglycans) and platelet factor 4 (PF4). PF4 is a platelet-specific
heparin-binding (neutralizing) protein that is abundant in platelet alpha granules from which it is secreted
following platelet stimulation. A reservoir of PF4 normally accumulates upon vascular endothelium.
Following heparin administration, immunogenic complexes of PF4 and heparin can provide an antigenic
stimulus for antibody development in some patients. Antibodies bound to platelets that display complexes of
PF4/heparin antigen can activate platelets via interaction of the Fc immunoglobulin tail of the IgG
antibody with platelet Fc gamma IIA receptors, leading to perpetuation of the pathologic process that can
cause platelet-rich thrombi in the microcirculation in some cases (eg, HITT syndrome). Functional assays
for HIT-II antibody detection rely on antibody-mediated heparin-dependent platelet activation, as detected
by platelet aggregation, or platelet secretion of serotonin or adenosine triphosphate (ATP) or other
substances, using patient serum or plasma supplemented with heparin and normal test platelets from
carefully selected donors. The sensitivity of functional assays for HIT-II ranges from 50% to 60% for
heparin-dependent platelet aggregation (HDSA) assays, to 70% to 80% for serotonin release assays. The
specificity of positive functional tests for HIT diagnosis is believed to be high (> or =90%). However,
because of their complexity, functional tests for detecting HIT antibodies are not widely available.
Enzyme-linked immunosorbent assays (ELISAs) have recently been developed to detect HIT-II antibodies
and are based on the detection of human antibodies that react with solid phase antigen complexes of
heparinoid and human PF4 (H/PF4 complexes). The ELISA for H/PF4 antibodies is very sensitive for
antibody detection, but relatively nonspecific for clinical HIT diagnosis. Routine screening of all patients
prior to, during, or following heparin use is currently not recommended. A positive H/PF4 ELISA result
has relatively low and uncertain predictive value for the development of clinical HIT-II.
diagnosis of HIT when clinical suspicion remains high. A functional assay for HIT antibodies (eg, heparin-dependent platelet aggregation or serotonin release assay may be helpful in these circumstances). Call 800-533-1710 for ordering information. A positive result is indicative of the presence of H/PF4 complex antibodies. However, this test's specificity is as low as 20% to 50% for clinical diagnosis of HIT, depending on the patient population studied. For example, up to 50% of surgical patients and up to 20% of medical patients treated with heparin may develop H/PF4 antibodies as measured by ELISA, and only a small proportion (1%-5%) develop clinical HIT. Accordingly, this test does not confirm the diagnosis of HIT-II. The diagnosis must be made in conjunction with clinical findings, including evaluation for other potential causes of thrombocytopenia. The presence of H/PF4 antibodies likely increases the risk of clinical HIT, with risk probably partly dependent on associated medical and surgical conditions, but currently there are few data about relative risk of HIT in various populations with positive tests for H/PF4 antibodies.

**Reference Values:**
HIT ELISA:
<0.400

**HIT Interpretation:**
Negative


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**Hepatitis A IgG Antibody, Serum**

**Clinical Information:** Hepatitis A virus (HAV) is endemic throughout the world, occurring most commonly, however, in areas of poor hygiene and low socioeconomic conditions. The virus is transmitted primarily by the fecal-oral route, and it is spread by close person-to-person contact and by food- and water-borne epidemics. Outbreaks frequently occur in overcrowded situations and in high-density institutions and centers, such as prisons and health care or day care centers. Viral spread by parenteral routes (eg, exposure to blood) is possible but rare, because infected individuals are viremic for a short period of time (usually <3 weeks). There is little or no evidence of transplacental transmission from mother to fetus or transmission to newborn during delivery. In most cases, antibodies to HAV (anti-HAV) are detectable by the time that symptoms occur, usually 15 to 45 days after exposure. Initial antibodies consist almost entirely of the IgM subclass. HAV-specific IgM antibody level in serum usually falls to an undetectable level by 6 months after acute infection. HAV-specific IgG antibody level in serum rises quickly once the virus is cleared and may persist for many years.

**Useful For:** Detection of previous exposure or immunity to hepatitis A infection

**Interpretation:** This assay detects the presence of hepatitis A virus (HAV)-specific IgG antibody in serum. A negative result indicates the absence of HAV-specific IgG antibody, implying no past exposure or immunity to HAV infection. A positive result indicates the presence of HAV-specific IgG antibody from either vaccination or past exposure to hepatitis A virus.

**Reference Values:**
Unvaccinated: negative
Vaccinated: positive

See Viral Hepatitis Serologic Profiles in Special Instructions.

Hepatitis A IgM Antibody, Serum

**Clinical Information:** Hepatitis A virus (HAV) is endemic throughout the world, occurring most commonly, however, in areas of poor hygiene and low socioeconomic conditions. The virus is transmitted primarily by the fecal-oral route, and it is spread by close person-to-person contact and by food- and water-borne epidemics. Outbreaks frequently occur in overcrowded situations and in high-density institutions and centers, such as prisons and health care or day care centers. Viral spread by parenteral routes (e.g., exposure to blood) is possible but rare, because infected individuals are viremic for a short period of time (usually <3 weeks). There is little or no evidence of transplacental transmission from mother to fetus or transmission to newborn during delivery. Serological diagnosis of acute viral hepatitis A depends on the detection of specific anti-HAV IgM. Its presence in the patient's serum indicates a recent exposure to HAV. HAV-specific IgM antibody level becomes detectable in the blood by 4 weeks after infection, persisting at elevated levels for about 2 months before declining to undetectable levels by 6 months. They rarely persist beyond 12 months after infection.

**Useful For:** Diagnosis of acute or recent hepatitis A infection

**Interpretation:** This assay detects the presence of hepatitis A virus (HAV)-specific IgM antibody in serum. Negative results indicate either 1) inadequate or delayed anti-HAV IgM response after known exposure to HAV, or 2) absence of acute or recent hepatitis A. Equivocal results may be seen in early acute hepatitis A associated with rising anti-HAV IgM levels or recent hepatitis A infection associated with declining anti-HAV IgM levels. Retesting for both anti-HAV IgM (HAVM / Hepatitis A IgM Antibody, Serum) and anti-HAV IgG (HAIGG / Hepatitis A IgG Antibody, Serum) in 2 to 4 weeks is recommended to determine the definitive HAV infection status. Positive results indicate acute or recent (<6 months) hepatitis A infection. As required by laws in almost all states, positive anti-HAV IgM test results must be urgently reported to state health departments for epidemiologic investigations of possible outbreak transmission.

**Reference Values:**
Negative

See Viral Hepatitis Serologic Profiles in Special Instructions.

**Clinical References:**

Hepatitis A Qualitative PCR HAV SuperQual

**Clinical Information:** The direct detection of HAV is a valuable tool in determining whether a patient undergoing therapeutic treatment has cleared the virus. It is also useful in determining whether blood or blood products are free of detectable HAV prior to distribution to patients. PCR is able to directly detect HAV RNA and does not rely on later markers such as antigens and antibodies that are not produced in newly infected individuals.

**Useful For:** Detect and quantify Hepatitis A Virus DNA (HAV DNA).

**Interpretation:** The presence of target-specific nucleic acid is indicative of infection. Mean Detection: 24.98 copies/mL (12.81 IU/mL) 95% Detection Cutoff: 61.83 copies/mL (31.71 IU/mL)

**Reference Values:**
Negative

Hepatitis B Core (HBc) Immunostain, Technical Component
**Only**

**Clinical Information:** Hepatitis B core antigen (HBcAg) labels the nuclei of hepatocytes that are infected with hepatitis B virus. The complete infective virion consists of a core of double stranded DNA, a specific DNA polymerase, and structural proteins. The nucleocapsid contains 2 serologically distinct antigens, the core antigen (HBcAg) and "e" antigen (HBeAg). These are surrounded by an outer envelope of surface protein that is recognized serologically as hepatitis B virus surface antigen (HBsAg). The demonstration of core antigen implies viral replication and therefore infectivity. Core antigen is most often demonstrated in chronic active hepatitis, compared to surface antigen in the carrier state.

**Useful For:** Aids in the identification of hepatitis B infection (chronic active state)

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Reference Values:**
N/A

**Clinical References:**

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**Hepatitis B Core Antibody, IgM, Serum**

**Clinical Information:** Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. In the initial (acute) phase of infection, antihepatitis B core antibodies (anti-HBc) consist almost entirely of the IgM antibody class and appear shortly after the onset of symptoms. Anti-HBc IgM antibody can be detected in serum and is usually present for up to 6 months after acute HBV infection. Anti-HBc IgM may be the only serologic marker of a recent hepatitis B infection detectable following the disappearance of hepatitis B surface antigen (HBsAg) and prior to the appearance of hepatitis B surface antibody (anti-HBs) (ie, serologic window period). See Viral Hepatitis Serologic Profile in Special Instructions.

**Useful For:** Diagnosis of acute hepatitis B infection Identifying acute hepatitis B virus (HBV) infection in the serologic window period when hepatitis B surface antigen (HBsAg) and antihepatitis B surface (anti-HBs) are negative Differentiation between acute and chronic or past hepatitis B infection in the presence of positive antihepatitis B core.

**Interpretation:** A positive result indicates recent acute hepatitis B infection. A negative result suggests lack of recent exposure to the virus in preceding 6 months.

**Reference Values:**
Negative

See Viral Hepatitis Serologic Profiles in Special Instructions.

**Hepatitis B Core Total Antibodies, Serum**

**Clinical Information:** Hepatitis B core antibodies (anti-HBc Ab) appear shortly after the onset of symptoms of hepatitis B infection and soon after the appearance of hepatitis B surface antigen (HBsAg). Initially, anti-HBc Ab consist almost entirely of the IgM class, followed by appearance of anti-HBc IgG, for which there is no commercial diagnostic assay. The anti-HBc total antibodies test, which detects both IgM and IgG antibodies, and the test for anti-HBc IgM antibodies may be the only markers of a recent hepatitis B infection detectable in the "window period." The window period begins with the clearance of HBsAg and ends with the appearance of antibodies to hepatitis B surface antigen (anti-HBs Ab). Anti-HBc total Ab may be the only serologic marker remaining years after exposure to hepatitis B. This assay is FDA-approved for in vitro diagnostic use and not for screening cell, tissue, and blood donors.

**Useful For:** Diagnosis of recent or past hepatitis B infection Determination of occult hepatitis B infection in otherwise healthy hepatitis B virus (HBV) carriers with negative test results for hepatitis B surface antigen, anti-hepatitis B surface, anti-hepatitis B core IgM, hepatitis Be antigen, and anti-HBe. This assay is not useful for differentiating among acute, chronic, and past or resolved hepatitis B infection.

**Interpretation:** A positive result indicates acute, chronic, or past or resolved hepatitis B. An inconclusive result suggests the presence of interfering substance in the patient’s serum specimen. Positive anti-hepatitis B core (anti-HBc) total test results should be correlated with the presence of other hepatitis B virus serologic markers, elevated liver enzymes, clinical signs and symptoms, and a history of risk factors. If clinically indicated, testing for HBIM / Hepatitis B Core Antibody, IgM, Serum is necessary to confirm an acute or recent infection. Neonates (<1 month old) with positive anti-HBc total results from this assay should be tested for anti-HBc IgM (HBIM / Hepatitis B Core Antibody, IgM, Serum) to rule out possible maternal anti-HBc causing false-positive results. Repeat testing using this assay for anti-HBc total within 1 month is also recommended in these neonates.

**Reference Values:**
- Negative
- Interpretation depends on clinical setting.

**See Viral Hepatitis Serologic Profiles in Special Instructions.**


**CORAB**

**Hepatitis B Core Total Antibodies, with Reflex to Hepatitis B Core Antibody IgM, Serum**

**Clinical Information:** During the course of a typical case of acute hepatitis B viral (HBV) infection, IgM antibodies to hepatitis B core antigen (anti-HBc IgM) are present in the serum shortly before clinical symptoms appear. Anti-HBc total is detectable during the prodromal, acute, and early convalescent phases when it exists as immunoglobulin M (IgM) anti-HBc. Anti-HBc IgM rises in level and is present during the core window period, ie, after hepatitis B surface antigen disappears and before antibodies to hepatitis B surface antigen appear. Anti-HBc total may be the only serologic marker remaining years after exposure to HBV.
Useful For: Detection and differentiation between recent and past/resolved or chronic hepatitis B viral (HBV) infection. Diagnosis of recent HBV infection during the "window period" when both hepatitis B surface antigen and antibodies to hepatitis B surface antigen are negative. Not useful for determining immunity to or recovery from hepatitis B viral (HBV) infection.

Interpretation: A positive, antibodies to hepatitis B core antigen (anti-HBc) total result may indicate, either, recent, past/resolved, or chronic hepatitis B viral (HBV) infection. Testing for anti-HBc IgM (HBIM / Hepatitis B Core Antibody, IgM, Serum) is necessary to confirm the presence of acute or recent hepatitis B. A negative anti-HBc total result with a positive anti-HBc IgM result indicates past or chronic HBV infection. Differentiation between past/resolved and chronic hepatitis B can be based on the presence of hepatitis B surface antigen in the latter condition. Negative anti-HBc total results indicate the absence of recent, past/resolved, or chronic hepatitis B. An inconclusive result for Hepatitis B core total HBC suggests presence of interfering substance in the patient’s serum specimen. Positive antibodies to hepatitis B core antigen (anti-HBc) total results with negative anti-HBc IgM results in infants younger than 18 months may be due to passively acquired maternal IgG antibodies. Additional testing, such as hepatitis B surface antigen, anti-HBc IgM, and hepatitis Be antigen, are necessary to confirm a diagnosis of acute or recent hepatitis B in these infants.

Reference Values:
Negative
Interpretation depends on clinical setting.
See Viral Hepatitis Serologic Profiles in Special Instructions.


Hepatitis B e-Antibody, Serum

Clinical Information: During recovery from acute hepatitis B, the hepatitis B e-antigen (HBeAg) level declines and becomes undetectable and hepatitis B e-antibody (anti-HBe) appears in the serum. Anti-HBe usually remains detectable for several years after recovery from acute infection. In hepatitis B virus (HBV) carriers and in patients with chronic hepatitis B, positive anti-HBe results usually indicate inactivity of the virus and low infectivity of the patients. Positive anti-HBe results in the presence of detectable HBV DNA in serum indicate active viral replication. See HBV Infection-Diagnostic Approach and Management Algorithm and Viral Hepatitis Serologic Profiles in Special Instructions.

Useful For: Determining infectivity of hepatitis B virus (HBV) carriers Monitoring infection status of individuals with chronic hepatitis B Monitoring serologic response of chronically HBV-infected patients receiving antiviral therapy Determining the level of hepatitis B e-antibody

Interpretation: Absence of hepatitis B e-antigen (HBeAg) with appearance of HBe antibody (anti-HBe) is consistent with inactivity of the virus and loss of hepatitis B virus (HBV) infectivity. Although resolution of chronic HBV infection generally follows the appearance of anti-HBe, the HBV carrier state may persist.

Reference Values:
Negative
See Viral Hepatitis Serologic Profiles in Special Instructions.

Hepatitis B e-Antigen and Hepatitis B e-Antibody, Serum

Clinical Information: Hepatitis B e-antigen (HBeAg) is a small polypeptide that exists in a free form in the serum of individuals during the early phase of hepatitis B infection, soon after hepatitis B surface antigen (HBsAg) becomes detectable. Serum levels of both HBeAg and HBsAg rise rapidly during the period of viral replication. The presence of HBeAg in serum correlates with hepatitis B virus (HBV) infectivity, the number of infectious virions, and the presence of HBV core antigen in the infected hepatocytes. During recovery from acute hepatitis B, HBeAg level declines and becomes undetectable in the serum, while hepatitis B e-antibody (anti-HBe) appears and becomes detectable in the serum. Anti-HBe usually remains detectable for many years after recovery from acute HBV infection. In HBV carriers and patients with chronic hepatitis B, positive HBeAg results usually indicate presence of active HBV replication and high infectivity. A negative HBeAg result indicates very minimal or no HBV replication. Positive anti-HBe results usually indicate inactivity of the virus and low infectivity. Positive anti-HBe results in the presence of detectable HBV DNA in serum also indicate active viral replication in these patients.

Useful For: Determining infectivity of hepatitis B virus (HBV) carriers Monitoring infection status of individuals with chronic hepatitis B Monitoring serologic response of chronically HBV-infected patients receiving antiviral therapy Determining the levels of both hepatitis B e-antigen and antibody

Interpretation: Presence of hepatitis B e-antigen (HBeAg) and absence of HBe antibody (anti-HBe) usually indicate active hepatitis B virus (HBV) replication and high infectivity. Absence of HBeAg with appearance of anti-HBe is consistent with loss of HBV infectivity. Although resolution of chronic HBV infection generally follows the appearance of anti-HBe, the HBV carrier state may persist.

Reference Values:
HEPATITIS Be ANTIGEN
Negative

HEPATITIS Be ANTIBODY
Negative

See Viral Hepatitis Serologic Profiles in Special Instructions.


Hepatitis B e-Antigen, Serum

Clinical Information: Hepatitis B e-antigen (HBeAg) is found in the early phase of hepatitis B infection soon after hepatitis B surface antigen becomes detectable. Serum levels of both antigens rise rapidly during the period of viral replication. The presence of HBeAg correlates with hepatitis B virus (HBV) infectivity, the number of infectious virions, and the presence of HBV core antigen in the infected hepatocytes. In HBV carriers and patients with chronic hepatitis B, positive HBeAg results usually indicate presence of active HBV replication and high infectivity. A negative HBeAg result indicates very minimal or no HBV replication. See Viral Hepatitis Serologic Profiles and HBV Infection-Diagnostic Approach and Management Algorithm in Special Instructions.

Useful For: Determining infectivity of hepatitis B virus (HBV) carriers Monitoring infection status of individuals with chronic hepatitis B Monitoring serologic response of chronically HBV-infected patients receiving antiviral therapy Determining the level of hepatitis B e-antigen

Interpretation: Presence of hepatitis B e-antigen (HBeAg) and absence of HBe antibody (anti-HBe) usually indicate active hepatitis B virus (HBV) replication and high infectivity. Absence of HBeAg with
appearance of anti-HBe is consistent with loss of HBV infectivity.

Reference Values:
Negative
See Viral Hepatitis Serologic Profiles in Special Instructions.


HBABY 63137

Hepatitis B Perinatal Exposure Follow-up Panel, Serum

Clinical Information: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. After a course of acute illness, HBV persists in about 10% of patients who were infected during adulthood. Some carriers are asymptomatic, others may develop chronic liver disease including cirrhosis and hepatocellular carcinoma. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted transplacentally. Infection of the infant can occur if the mother is a chronic hepatitis B surface antigen (HBsAg) carrier or has an acute HBV infection at the time of delivery. Transmission is rare if an acute infection occurs in either the first or second trimester of pregnancy. Without postexposure prophylaxis (a combination of HBV vaccination and hepatitis B immune globulin), the risk of an infant acquiring HBV from an infected mother as a result of perinatal exposure is 70% to 90% for infants born to mothers who are positive for HBsAg and hepatitis B e antigen (HBeAg). The risk is 5% to 20% for infants born to HBsAg-positive but HBeAg-negative mothers. HBV is also spread primarily through percutaneous contact with infected blood products (ie, blood transfusion, sharing of needles by drug addicts). The virus is found in virtually every type of human body fluid and also is spread through oral and genital contact. See the following in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -Viral Hepatitis Serologic Profile

Useful For: Determining hepatitis B virus infection and immunity status (with or without perinatal prophylaxis) in infants born to mothers with chronic hepatitis B

Interpretation: Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in blood 6 to 16 weeks after exposure to HBV. A confirmed positive HBsAg result is indicative of acute or chronic hepatitis B. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6-months duration indicates development of either a chronic carrier state or chronic hepatitis B. Hepatitis B surface antibody (HBsAb) appears with the resolution of HBV infection and disappearance of HBsAg. A positive result indicates recovery from acute or chronic hepatitis B, or acquired immunity from HBV vaccination. This assay does not differentiate between a vaccine-induced immune response and recovery from HBV infection. Per assay manufacturer’s instructions for use, positive results are defined as HBsAb levels of 12.0 mIU/mL or greater, with adequate immunity to hepatitis B after recovery from past infection or HBV vaccination. Per current CDC guidance, individuals with HBsAb levels of 10 mIU/mL or greater after completing an HBV vaccination series are considered protected from hepatitis B.(1) Negative results, defined as HBsAb levels of less than 5.0 mIU/mL, indicate a lack of recovery from acute or chronic hepatitis B or inadequate immune response to HBV vaccination. Indeterminate results, defined as HBsAb levels in the range of 5.0 to 11.9 mIU/mL, indicate inability to determine if HBsAb is present at levels consistent with recovery or immunity. Repeat testing is recommended in 1 to 3 months. Hepatitis B core (HBe) total antibodies (combined IgG and IgM) appear shortly after the onset of symptoms of HBV infection and may be the only serologic marker remaining years after exposure to HBV. A positive result indicates exposure to HBV infection. A positive HBsAb result along with a positive HBe total antibody result is indicative of recovery from HBV infection. A positive HBsAb result with a negative HBe total antibody result is consistent with immunity to hepatitis B from HBV vaccination. See the following in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -Viral Hepatitis Serologic Profiles
HBABT 87893

Hepatitis B Surface Antibody Monitor, Post-Transplant, Serum

**Clinical Information:** For patients with chronic hepatitis B virus (HBV) infection (hepatitis B surface antigen-positive), outcomes following liver transplantation for end-stage liver disease are poor. Recurrent HBV disease is common and associated with decreased liver graft and patient survival (approximately 50% at 5 years). Studies have shown administration of hepatitis B immune globulin (HBIG) in the perioperative and early posttransplant periods could delay or prevent recurrent HBV infection in these transplant recipients. Intravenous or intramuscular administration of HBIG has become the standard of care for these liver transplant recipients in most liver transplant programs in the United States since mid-1990. Most therapy protocols administer HBIG in high doses (10,000 IU) during the perioperative period and first week after transplantation, with the goal of achieving serum hepatitis B surface antibody (anti-HBs) levels of above 500 mIU/mL. Serial levels of anti-HBs are obtained to determine the pharmacokinetics of HBIG in each patient to guide frequency of HBIG dosing. There is a high degree of variability in HBIG dosage required to achieve desirable serum anti-HBs levels among transplant recipients during the first few weeks to months after transplantation. Patients who were hepatitis Be (HBe)-antigen positive before transplantation usually require more HBIG to achieve the target anti-HBs levels, especially in the first week after transplantation. Duration of HBIG therapy varies from 6 months to indefinite among different US liver transplant programs. Protocols providing less than 12 months of therapy usually combine HBIG with another effective anti-HBV agent such as lamivudine. See HBV Infection-Monitoring Before and After Liver Transplantation in Special Instructions.

**Useful For:** Monitoring serum anti-hepatitis B surface (anti-HBs) levels during intravenous or intramuscular hepatitis B immune globulin (HBIG) therapy to prevent hepatitis B virus (HBV) reinfection in liver transplant recipients with known previous chronic hepatitis B virus (HBV)

**Interpretation:** Please refer to health care provider's institutional hepatitis B immune globulin (HBIG) therapy protocol for desirable hepatitis B surface antibody (anti-HBs) levels. Studies indicated that serum anti-HBs levels needed to prevent hepatitis B virus (HBV) reinfection were greater than 500 mIU/mL during the first week after transplantation, greater than 250 mIU/mL during weeks 2 to 12, and greater than 100 mIU/mL after week 12. See HBV Infection-Monitoring Before and After Liver Transplantation in Special Instructions.

**Reference Values:**
Not applicable


HBAB 8254

Hepatitis B Surface Antibody, Qualitative/Quantitative, Serum

**Clinical Information:** Hepatitis B virus (HBV) infection, also known as serum hepatitis, is...
endemic throughout the world. The infection is spread primarily through blood transfusion or percutaneous contact with infected blood products, such as sharing of needles among injection drug users. The virus is also found in virtually every type of human body fluid and has been known to be spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but is not commonly transmitted via the transplacental route. The incubation period for HBV infection averages 60 to 90 days (range of 45-180 days). Common symptoms include malaise, fever, gastroenteritis, and jaundice (icterus). After acute infection, HBV infection becomes chronic in 30% to 90% of infected children younger than 5 years of age and in 5% to 10% of infected individuals age 5 or older. Some of these chronic carriers are asymptomatic, while others progress to chronic liver disease, including cirrhosis and hepatocellular carcinoma. Hepatitis B surface antigen (HBsAg) is the first serologic marker, appearing in the serum 6 to 16 weeks following HBV infection. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms with the appearance of hepatitis B surface antibody (anti-HBs). Anti-HBs also appears as the immune response following hepatitis B vaccination. See HBV Infection-Diagnostic Approach and Management Algorithm in Special Instructions

**Useful For:** Identifying previous exposure to hepatitis B virus Determining adequate immunity from hepatitis B vaccination

**Interpretation:** This assay provides both qualitative and quantitative results. A positive result indicates recovery from acute or chronic hepatitis B virus (HBV) infection or acquired immunity from HBV vaccination. This assay does not differentiate between a vaccine-induced immune response and an immune response induced by infection with HBV. A positive total antihepatitis B core (anti-HBc) result would indicate that the hepatitis B surface antibody (anti-HBs) response is due to past HBV infection. Per assay manufacturer's instructions for use, positive results, defined as anti-HBs levels of 12.0 mIU/mL or greater, indicate adequate immunity to hepatitis B from past hepatitis B or HBV vaccination. However, per current CDC guidance,(1) individuals with anti-HBs levels of 10 mIU/mL or greater after completing an HBV vaccination series are considered protected from hepatitis B. Negative results, defined as anti-HBs levels of <5.0 mIU/mL, indicate a lack of recovery from acute or chronic hepatitis B or inadequate immune response to HBV vaccination. The US Advisory Committee on Immunization Practices does not recommend more than 2 HBV vaccine series in nonresponders. Indeterminate results, defined as anti-HBs levels in the range from 5 to 11.9 mIU/mL, indicate inability to determine if anti-HBs is present at levels consistent with recovery or immunity. Repeat testing is recommended in 1 to 3 months. See HBV Infection-Diagnostic Approach and Management Algorithm in Special Instructions.

**Reference Values:**

**HEPATITIS B SURFACE ANTIBODY**
- Unvaccinated: negative
- Vaccinated: positive

**HEPATITIS B SURFACE ANTIBODY, QUANTITATIVE**
- Unvaccinated: <5.0 mIU/mL
- Vaccinated: ≥ 12.0 mIU/mL

See Viral Hepatitis Serologic Profiles in Special Instructions.

**Clinical References:**
1. CDC. Immunization of health-care personnel. Mortal Morbid Wkly Rpt 2011;60[No. SS-7]:5
2. Immunization of Health-Care Personnel. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Centers for Disease Control and Prevention, MMWR 2011;60(7):5
B-infected hepatocytes in a granular pattern. The complete infective virion consists of a core of double-stranded DNA, a specific DNA polymerase, and structural proteins. The nucleocapsid contains 2 serologically distinct antigens, the core antigen (HBcAg) and "e" antigen (HBeAg). These are surrounded by an outer envelope of surface protein that is recognized serologically as hepatitis B virus surface antigen. Core antigen is most often demonstrated in chronic active hepatitis, compared to surface antigen in the carrier state.

**Useful For:** Aids in the identification of hepatitis B infection (carrier state)

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**HBNTP 35936**

**Hepatitis B Surface Antigen Confirmation Prenatal, Serum**

**Clinical Information:** Hepatitis B virus (HBV) is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (eg, blood transfusion, sharing of needles by intravenous drug addicts). The virus is also found in various human body fluids, and it is known to be spread through oral and genital contacts. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted transplacentally. Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum at 6 to 16 weeks following exposure to HBV. In acute infection, HBsAg usually disappears in 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6 months in duration indicates development of either a chronic carrier state or chronic HBV infection. See The Laboratory Approach to the Diagnosis and Monitoring of Hepatitis B Infection in Publications. See the following in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -HBV Infection-Monitoring Before and After Liver Transplantation -Viral Hepatitis Serologic Profile

**Useful For:** Diagnosis of acute, recent, or chronic hepatitis B infection in prenatal patients

**Interpretation:** A reactive screen result confirmed as positive by hepatitis B surface antigen (HBsAg) confirmatory test is indicative of acute or chronic hepatitis B virus (HBV) infection, or chronic HBV carrier state. Specimens with reactive screen results but negative (ie, not confirmed) HBsAg confirmatory test results are likely to contain cross-reactive antibodies from other infectious or immunologic disorders. Repeat testing is recommended at a later date if clinically indicated. Confirmed presence of HBsAg is frequently associated with HBV replication and infectivity, especially when accompanied by presence of hepatitis B envelope (HBe) antigen and/or detectable HBV DNA. See the following in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -HBV Infection-Monitoring Before and After Liver Transplantation -Viral Hepatitis Serologic Profile
HBAGP 86185

**Hepatitis B Surface Antigen Prenatal, Serum**

**Clinical Information:** Hepatitis B virus (HBV) is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (e.g., blood transfusion, sharing of needles by intravenous drug addicts). The virus is also found in various human body fluids, and it is known to be spread through oral and genital contacts. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted transplacentally. Infection of the infant can occur if the mother is a chronic hepatitis B surface antigen carrier or has an acute HBV infection at the time of delivery. Transmission is rare if an acute infection occurs in either the first or second trimester of pregnancy.

**Useful For:** Stand-alone prenatal screening test for chronic hepatitis B in pregnant women

**Interpretation:** A reactive screen result confirmed as positive by hepatitis B surface antigen (HBsAg) confirmatory test is indicative of acute or chronic hepatitis B virus (HBV) infection, or chronic HBV carrier state. Specimens with initially reactive test results, but negative (not confirmed) by HBsAg confirmation test, are likely to contain cross-reactive antibodies from other infectious or immunologic disorders. These unconfirmed HBsAg-reactive screening test results should be interpreted in conjunction with test results of other HBV serologic markers (e.g., hepatitis B surface antibody; hepatitis B core antibody, total and IgM). The presence of HBsAg is frequently associated with HBV replication and infectivity, especially when accompanied by the presence of hepatitis Be antigen (HBe) and/or detectable HBV DNA.

**Reference Values:**

Negative

See Viral Hepatitis Serologic Profiles in Special Instructions.


HBAG 9013

**Hepatitis B Surface Antigen, Serum**

**Clinical Information:** Hepatitis B virus (HBV) is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (e.g., blood transfusion, sharing of needles by intravenous drug addicts). The virus is also found in various human body fluids, and it is known to be spread through oral and genital contacts. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted transplacentally. Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum at 6 to 16 weeks following exposure to HBV. In acute infection, HBsAg usually disappears in 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6 months in duration indicates development of either a chronic carrier state or chronic HBV infection. See the following in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -HBV Infection-Monitoring Before and After Liver Transplantation -Viral Hepatitis Serologic Profile
Useful For: Diagnosis of acute, recent, or chronic hepatitis B infection Determination of chronic hepatitis B infection status

Interpretation: A reactive screen result (signal-to-cutoff ratio: S/CO ≥ 1.00, but < or =100.0) confirmed as positive by hepatitis B surface antigen (HBsAg) confirmatory test (see Method Description) or a positive screen result (S/CO > 100.0) is indicative of acute or chronic hepatitis B virus (HBV) infection, or chronic HBV carrier state. Specimens with reactive screen results but negative (ie, not confirmed) HBsAg confirmatory test results are likely to contain cross-reactive antibodies from other infectious or immunologic disorders. Repeat testing is recommended at a later date if clinically indicated. Confirmed presence of HBsAg is frequently associated with HBV replication and infectivity, especially when accompanied by presence of hepatitis Be antigen (HBe) and/or detectable HBV DNA. See the following in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -HBV Infection-Monitoring Before and After Liver Transplantation -Viral Hepatitis Serologic Profile

Reference Values:
Negative
See Viral Hepatitis Serologic Profiles in Special Instructions.

Clinical References:

Hepatitis B Virus (HBV) DNA Detection and Quantification by Real-Time PCR, Serum

Clinical Information: Diagnosis of acute or chronic hepatitis B virus (HBV) infection is based on the presence of HBV serologic markers such as hepatitis B surface antigen (HBsAg) and hepatitis B core IgM antibody (anti-HBc IgM), or the presence of HBV DNA detected by molecular assays. Although the diagnosis of acute and chronic HBV infection is usually made by serologic methods, detection and quantification of HBV DNA in serum are useful to:-Diagnose some cases of early acute HBV infection (before the appearance of HBsAg) -Distinguish active from inactive HBV infection -Monitor a patient's response to anti-HBV therapy The presence of HBV DNA in serum is a reliable marker of active HBV replication. HBV DNA levels are detectable by 30 days following infection, generally reach a peak at the time of acute hepatitis, and gradually decrease and disappear when the infection resolves spontaneously. In cases of acute viral hepatitis with equivocal HBsAg test results, testing for HBV DNA in serum may be a useful adjunct in the diagnosis of acute HBV infection, since HBV DNA can be detected approximately 21 days before HBsAg typically appears in the serum. Patients with chronic HBV infection fail to clear the virus and remain HBsAg-positive. Such cases may be further classified as chronic active (replicative) HBV (high HBV levels, hepatitis Be antigen [HBeAg]-positive) or chronic inactive (nonreplicative) HBV (low or undetectable HBV DNA levels, HBeAg-negative). HBV DNA levels in serum are useful in determining the status of chronic HBV infection, by differentiating between active and inactive disease states. Patients with chronic active HBV are at greater risk for more serious liver disease and are more infectious than patients with inactive HBV infection. Reactivation of inactive chronic HBV infection (HBeAg-negative state) may occur with or without reappearance of HBeAg in serum. In patients with HBeAg-negative disease, detection of HBV DNA is the only reliable marker of active HBV replication. The therapeutic goal of anti-HBV therapy in patients who are HBeAg-positive is to achieve long-term suppression of viral replication with undetectable HBV DNA, HBe seroconversion and loss of HBeAg. The therapeutic goal in patients with HBeAg-negative disease is typically long-term viral suppression. The emergence of drug-resistant HBV strains in response to treatment with nucleoside/nucleotide analogs (eg, lamivudine, adefovir, entecavir, tenofovir), is characterized by either the reappearance of HBV DNA in serum (after it had become undetectable) or an increase in HBV DNA levels (following an initial decline). The following algorithms are available in Special Instructions: HBV Infection-Diagnostic Approach and Management Algorithm HBV Infection-Monitoring Before and After Liver Transplantation
**Useful For:** Detection and quantification of hepatitis B virus (HBV) DNA in serum of patients with chronic HBV infection (ie, hepatitis B surface antigen-positive) Monitoring disease progression in chronic HBV infection Monitoring response to anti-HBV therapy

**Interpretation:** The quantification range of this assay is 10 to 1,000,000,000 IU/mL (1.00 log to 9.00 log IU/mL). An “Undetected” result indicates that hepatitis B virus (HBV) DNA was not detected in the serum specimen. A result of “<10 IU/mL (<1.00 log IU/mL)” indicates that HBV DNA is detected, but the HBV DNA level present cannot be quantified accurately below this lower limit of quantification of this assay. When clinically indicated, follow-up testing with this assay is recommended in 1 to 2 months. A quantitative result expressed in IU/mL and log IU/mL indicates the degree of active HBV viral replication in the patient. Monitoring HBV DNA levels over time is important for assessing disease progression or monitoring a patient's response to anti-HBV therapy. A result of “>1,000,000,000 IU/mL (>9.00 log IU/mL)” indicates the presence of active HBV viral replication, and the HBV DNA level present cannot be quantified accurately above this upper limit of quantification of this assay. An “Inconclusive” result with the comment “Submit a new specimen for testing if clinically indicated” indicates that inhibitory substances may be present in the specimen. When clinically indicated, collection and testing of a new specimen is recommended.

**Reference Values:**

Undetected

**Clinical References:**


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**Hepatitis B Virus Genotyping**

**Reference Values:**

Interpretive Information: Hepatitis B Virus Genotype

HBV genotype and resistance interpretation is provided by SeqHepB software from Evivar Medical. The following mutations are reported: reverse transcriptase L80I/V, I69T, V173L, L180M, A181S/T/V, T184A/C/F/I/G/S/M/L, S202C/G/I, M204I/V, N236T, M250I/L/V; surface antigen P120T, D144A, G145R.

Both the HBV RT polymerase and the HBsAg encoding regions are sequenced. Resistance and surface antigen mutations are reported. In addition, the major HBV genotypes are identified. Mutations in viral sub-populations below 20% of total may not be detected.

This test is performed pursuant to a license agreement with Roche Molecular Systems, Inc.

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**Hepatitis Bs Antigen (HBsAg) for Cadaveric or Hemolyzed Specimens, Serum**

**Clinical Information:** Hepatitis B virus (HBV) is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (eg, blood transfusion, sharing of needles by intravenous drug addicts). The virus is also found in various human body fluids, and it is known to be spread through oral and genital contacts. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted...
transplacentally. Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum at 6 to 16 weeks following HBV infection. In acute infection, HBsAg usually disappears in 1 to 2 months after the onset of symptoms. Persistence of HBsAg for greater than 6 months indicates development of either a chronic carrier or chronic HBV infection.

**Useful For:** Testing cadaveric and hemolyzed blood specimens for hepatitis B surface antigen; FDA-licensed for use with hemolyzed specimens Diagnosis of acute, recent (<6 month duration), or chronic hepatitis B infection; determination of chronic hepatitis B carrier status

**Interpretation:** A positive result (reactive screening and confirmed positive by neutralization test; see Method Description) is indicative of acute or chronic hepatitis B virus (HBV) infection, or chronic HBV carrier state. A positive (confirmed) neutralization test result is considered the definitive test result for hepatitis B surface antigen (HBsAg). Specimens that are reactive by the screening test but negative (not confirmed) by the neutralization test are likely to contain cross-reactive antibodies from other infectious or immunologic disorders. These unconfirmed HBsAg screening test results should be interpreted in conjunction with test results of other HBV serological markers (eg, anti-hepatitis B surface antibody, anti-hepatitis B core total antibody). The presence of HBsAg is frequently associated with HBV infectivity, especially when accompanied by the presence of hepatitis Be antigen or HBV DNA.

**Reference Values:**
Negative

**Clinical References:**

**Hepatitis C Antibody Screen with Reflex to HCV RNA by PCR, Serum**

**Clinical Information:** Hepatitis C virus (HCV) is recognized as the cause of most cases of posttransfusion hepatitis and is a significant cause of morbidity and mortality worldwide. In the United States, HCV infection is quite common, with an estimated 3.5 to 4 million chronic HCV carriers. Laboratory testing for HCV infection usually begins by screening for the presence of HCV-specific antibodies in serum, using an FDA-approved screening test. Specimens that are repeatedly reactive by screening tests should be confirmed with HCV tests with higher specificity, such as direct detection of HCV RNA by reverse transcription-PCR (RT-PCR) or HCV-specific antibody confirmatory tests. HCV antibodies are usually not detectable during the first 2 months following infection, but they are usually detectable by the late convalescent stage (>6 months after onset) of infection. These antibodies do not neutralize the virus and they do not provide immunity against this viral infection. Decrease in the HCV antibody level in serum may occur following resolution of infection. Current screening serologic tests to detect antibodies to HCV include EIA and chemiluminescence immunoassays. Despite the value of serologic tests to screen for HCV infection, several limitations of serologic testing exist: -There may be a long delay (up to 6 months) between exposure to the virus and the development of detectable HCV-specific antibodies -False-reactive screening test result can occur -A reactive screening test result does not distinguish between past (resolved) and present HCV infection -Serologic tests cannot provide information on clinical response to anti-HCV therapy Reactive screening test results should be followed by a supplemental or confirmatory test, such as a nucleic acid test for HCV RNA or HCV antibody confirmatory test. Nucleic acid tests provide a very sensitive and specific approach for the direct detection of HCV RNA. See Hepatitis C: Testing Algorithm for Screening and Diagnosis in Special Instructions.

**Useful For:** Screening for hepatitis C in primary care settings in high-risk persons with a current or past history of illicit injection drug use or a history of receiving a blood transfusion prior to 1992 Screening for hepatitis C in primary care settings in non-high risk persons born from 1945 through 1965

Note: In accordance with National Coverage Determination guidance, this test is indicated for...
asymptomatic patients born from 1945 through 1965, those with a history of injection drug use, or a history of receiving blood transfusion prior to 1992.

**Interpretation:** Chemiluminescence Immunoassay: Reactive hepatitis C virus (HCV) antibody screening results with signal-to-cutoff (S/CO) ratios of below 8.0 are not predictive of the true HCV antibody status and additional testing is recommended to confirm HCV antibody status. Reactive results with S/CO ratios of 8.0 or greater are highly predictive (95% or greater probability) of the true HCV antibody status, but additional testing is needed to differentiate between past (resolved) and chronic hepatitis C. A negative screening test result does not exclude the possibility of exposure to or infection with HCV. Negative screening test results in individuals with prior exposure to HCV may be due to low antibody levels that are below the limit of detection of this assay or lack of reactivity to the HCV antigens used in this assay. Patients with acute or recent HCV infections (<3 months from time of exposure) may have false-negative HCV antibody results due to the time needed for seroconversion (average of 8 to 9 weeks). Testing for HCV RNA using HCVQN / Hepatitis C Virus (HCV) RNA Detection and Quantification by Real-Time Reverse Transcription-PCR (RT-PCR). Serum is recommended for detection of HCV infection in such patients. RT-PCR: The quantification range of this test is 15 to 100,000,000 IU/mL. Negative results indicate that HCV RNA is not detected in the serum. A numerical result indicates the presence of HCV infection with active viral replication. Positive results with the comment of “HCV RNA detected, but <15 IU/mL” indicate that the HCV RNA present is at a level below the quantifiable lower limit of this assay. Follow-up testing by this assay is recommended in 1 to 3 months. Positive results with the comment of “but >100,000,000 IU/mL” indicate that the level of HCV RNA present is above the quantifiable upper limit of this assay. A single negative HCV RNA result with positive HCV antibody status (assay signal-to-cutoff ratio of 3.8 or greater by EIA, or 8.0 or greater by chemiluminescence immunoassay), does not necessarily indicate past or resolved HCV infection. Individuals with such results should be retested for HCV RNA in 1 to 2 months, to distinguish between patients with past or resolved HCV infection and those with chronic HCV infection having episodic HCV replication. Presence of HCV antibodies (assay signal-to-cutoff ratio of <3.8 by EIA or <8.0 by chemiluminescence immunoassay) in individuals with negative HCV RNA results may be confirmed by HCVL / Hepatitis C Virus Antibody Confirmation, Serum.

**Reference Values:**
Negative
See Viral Hepatitis Serologic Profiles in Special Instructions.


**HCVDX**

**Hepatitis C Antibody with Reflex to HCV RNA by PCR, Serum**

**Clinical Information:** Hepatitis C virus (HCV) is recognized as the cause of most cases of posttransfusion hepatitis and is a significant cause of morbidity and mortality worldwide. In the United States, HCV infection is quite common, with an estimated 3.5 to 4 million chronic HCV carriers. Laboratory testing for HCV infection usually begins by screening for the presence of HCV antibodies in serum, using an FDA-approved screening test. Specimens that are repeatedly reactive by screening tests should be confirmed with HCV tests with higher specificity, such as direct detection of HCV RNA by reverse transcription-PCR (RT-PCR) or HCV-specific antibody confirmatory tests. HCV antibodies are usually not detectable during the first 2 months following infection, but they are usually detectable by the late convalescent stage (>6 months after onset) of infection. These antibodies do not neutralize the virus and they do not provide immunity against this viral infection. Decrease in the HCV antibody level in serum may occur after resolution of infection. Current screening serologic tests to detect antibodies to HCV include EIA and chemiluminescence immunoassay. Despite the value of serologic tests to screen for HCV infection, several limitations of serologic testing exist: -There may be a long delay (up to 6 months) between exposure to the virus and the development of a detectable HCV antibody -False-reactive screening test result can occur -A reactive screening test result does not distinguish between past
(resolved) and present HCV infection. Serologic tests cannot provide information on clinical response to anti-HCV therapy. Reactive screening test results should be followed by a supplemental or confirmatory test, such as nucleic acid test for HCV RNA or HCV antibody confirmatory test. Nucleic acid tests provide a very sensitive and specific approach for the direct detection of HCV RNA. See Hepatitis C: Testing Algorithm for Screening and Diagnosis in Special Instructions.

**Useful For:** Diagnosis of recent or chronic hepatitis C virus infection in symptomatic patients

**Interpretation:** Chemiluminescence Immunoassay: Reactive hepatitis C virus (HCV) antibody screening results with signal-to-cutoff (S/CO) ratios of below 8.0 are not predictive of the true HCV antibody status and additional testing is recommended to confirm anti-HCV status. Reactive results with S/CO ratios of 8.0 or greater are highly predictive (95% or greater probability) of the true anti-HCV status, but additional testing is needed to differentiate between past (resolved) and chronic hepatitis C. A negative screening test result does not exclude the possibility of exposure to or infection with HCV. Negative screening test results in individuals with prior exposure to HCV may be due to low antibody levels that are below the limit of detection of this assay or lack of reactivity to the HCV antigens used in this assay. Patients with acute or recent HCV infections (<3 months from time of exposure) may have false-negative HCV antibody results due to the time needed for seroconversion (average of 8 to 9 weeks). Testing for HCV RNA using HCVQN / Hepatitis C Virus (HCV) RNA Detection and Quantification by Real-Time Reverse Transcription-PCR (RT-PCR), Serum is recommended for detection of HCV infection in such patients. RT-PCR: The quantification range of this test is 15 to 100,000,000 IU/mL. Negative results indicate that HCV RNA is not detected in the serum. A numerical result indicates the presence of HCV infection with active viral replication. Positive results with the comment of "HCV RNA detected, but <15 IU/mL" indicate that the HCV RNA present is at a level below the quantifiable lower limit of this assay. Follow-up testing by this assay is recommended in 1 to 3 months. Positive results with the comment of "but >100,000,000 IU/mL" indicate that the level of HCV RNA present is above the quantifiable upper limit of this assay. A single negative HCV RNA result with positive HCV antibody status (assay signal-to-cutoff ratio of 3.8 or greater by EIA, or 8.0 or greater by chemiluminescence immunoassay), does not necessarily indicate past or resolved HCV infection. Individuals with such results should be retested for HCV RNA in 1 to 2 months, to distinguish between patients with past or resolved HCV infection and those with chronic HCV infection having episodic HCV replication. Presence of anti-HCV antibodies (assay signal-to-cutoff ratio of <3.8 by EIA or <8.0 by chemiluminescence immunoassay) in individuals with negative HCV RNA results may be confirmed HCVL / Hepatitis C Virus Antibody Confirmation, Serum.

**Reference Values:**
Negative

See Viral Hepatitis Serologic Profiles in Special Instructions.

**Clinical References:**
2. American Association for the Study of Liver Diseases and Infectious Diseases Society of America: HCV guidance: Recommendations for testing, managing, and treating hepatitis C. Available at www.hcvguidelines.org/full-report-view

**Hepatitis C Viral RNA Genotype 1 NS3 Drug Resist**

**Clinical Information:** The clinical significance for antiviral therapy of NS3 resistance associated variants may vary according to the clinical status and antiviral treatment experience of the HCV-infected patient.

**Reference Values:**
HCV NS3 Subtype: Not Predicted

**Hepatitis C Viral RNA Genotype 1 NS5a Drug Resistance**

**Clinical Information:** The clinical significance of NS5a resistance associated variants for antiviral
therapy may vary according to the clinical status and antiviral treatment experience of the HCV-infected patient. Testing for NS5a resistance-associated variants prior to initiation of treatment with elbasvir plus grazoprevir in HCV genotype 1a infected patients is recommended.

Reference Values:
HCV NS5a Subtype: Not Detected

Hepatitis C Viral RNA Genotype 1 NS5b Drug Resistance
Reference Values:
Reference Range:
HCV NS5b Subtype: Not detected

Hepatitis C Viral RNA Genotype 3 NS5a Drug Resistance
Clinical Information: The clinical significance for antiviral therapy of NS5a resistance associated variants may vary according to the clinical status and antiviral treatment experience of the HCV-infected patient.

Reference Values:
HCV NS5a Subtype: Not Predicted

Hepatitis C Virus (HCV) RNA Detection and Quantification by Real-Time Reverse Transcription-PCR (RT-PCR), Serum
Clinical Information: Of all individuals infected with hepatitis C virus (HCV), about 75% of them will develop chronic hepatitis C, with ongoing viral replication in the liver and detectable HCV RNA in serum or plasma, eventually resulting in cirrhosis. The remaining 25% of the infected individuals recover from the infection without evidence of viral replication or presence of detectable HCV RNA in serum or plasma. Chronic HCV infection can be cured at variable success rates with either combined interferon-alpha and ribavirin therapy or interferon-free combination of direct-acting antiviral (DAA) agents. The antiviral response rates correlate with pretreatment serum or plasma HCV RNA levels (viral load) and the HCV genotype found in the infected individuals. The optimal duration of combined interferon and ribavirin therapy can be determined from the patient's pretreatment viral load and HCV genotype. Clinical trial studies indicated that a decrease in HCV RNA levels of more than 2 log IU/mL at 4 weeks or 12 weeks of therapy is predictive of an increased chance of achieving a sustained virologic response (defined as undetectable HCV RNA levels in serum 6 months after completing antiviral therapy). Despite receiving longer duration of antiviral therapy (48 weeks versus 24 weeks), patients with chronic infection due to HCV genotypes 1 and 4 generally have less favorable sustained virologic response rates (40%-50%) than those infected with genotypes 2 and 3 (>80%). Due to the necessary prolonged duration (typically 24 to 48 week duration) and low cure rates of such antiviral therapy, interferon-based therapy has been supplanted with potent interferon-free DAA combination therapy now. Cure rates, as defined by sustained virologic response (SVR), of over 90% are observed among HCV-infected patients treated with interferon-free DAA combinations that are of shorter duration of treatment (eg, 8 or 12 weeks) than those of interferon-based therapy. Current guidelines for antiviral therapy of chronic hepatitis C recommend quantitative testing for HCV RNA in serum or plasma before initiating antiviral therapy, at 4 weeks of therapy, and at 12 weeks after completion of therapy. HCV RNA level of below 25 IU/mL in serum or plasma at 12 weeks after ending therapy is the therapeutic goal and indicates an SVR is achieved. Quantitative HCV RNA testing can be considered at the end of therapy and at 24 weeks or later after completion of antiviral therapy. The following algorithms are available in Special Instructions: -Hepatitis C: Testing Algorithm for Screening and Diagnosis -Chronic Hepatitis C Treatment and Monitoring Algorithm: Direct Antiviral Antigen (DAA) Combination (Interferon-Free)

Useful For: Detection of acute hepatitis C virus (HCV) infection before the appearance of HCV antibodies in serum (ie, <2 months from exposure) Detection and confirmation of chronic HCV infection...
Quantification of HCV RNA in serum of patients with chronic HCV infection (HCV antibody-positive)
Monitoring disease progression in chronic HCV infection and response to antiviral therapy Determining
cure and detection of relapse after completion of antiviral therapy

**Interpretation:** This assay has a result range of 15 to 100,000,000 IU/mL (1.18 log to 8.00 log
IU/mL) for quantification of hepatitis C virus (HCV) RNA in serum. An "Undetected" result indicates
that the HCV is absent in the patient's serum specimen. A result of "<15 IU/mL (<1.18 log IU/mL)"
indicates that HCV RNA is detected, but the HCV RNA level present cannot be quantified accurately
below this lower limit of quantification of this assay. When clinically indicated, follow-up testing with
this assay is recommended in 1 to 2 months. To assess response-guided therapy eligibility, an
"Undetected" result is required, and a result of "<15 IU/mL mL (<1.18 log IU/mL)" should not be
considered equivalent to an "Undetected" result. A quantitative result expressed in IU/mL and log
IU/mL indicates the degree of active HCV viral replication in the patient. Monitoring HCV RNA levels
over time is important to assess disease progression and/or monitoring a patient's response to anti-HCV
therapy. A result of ">100,000,000 IU/mL (>8.00 log IU/mL)" indicates the presence of active HCV
viral replication, and the HCV RNA level present cannot be quantified accurately above this upper limit
of quantification of this assay. An "Inconclusive" result reported with a comment indicates that testing
failed, likely due to presence of inhibitory substances in the submitted serum specimen. A new
specimen should be collected for retesting.

**Reference Values:**
Undetected

**Clinical References:** 1. de Leuw P, Sarrazin C, Zeuzem S: How to use virological tools for the
optimal management of chronic hepatitis C. Liver Int 2011;31 Suppl 1:3-12 2. Centers for Disease
Control and Prevention: Testing for HCV infection: an update of guidance for clinicians and
Study of Liver Diseases and Infectious Diseases Society of America: HCV guidance: Recommendations
for testing, managing, and treating hepatitis C. Accessed July 14, 2017 Available at
www.hcvguidelines.org/full-report-view

**Hepatitis C Virus Antibody Confirmation, Serum**

**Clinical Information:** Laboratory testing for hepatitis C virus (HCV) infection in patients and
donors of organ, blood, cells, tissue, and tissue products usually begins by screening for the presence
of HCV antibodies (anti-HCV) in serum, using an FDA-approved anti-HCV screening test. Specimens that
are repeatedly reactive by screening tests should be confirmed by more HCV-specific tests, such as
direct detection of HCV RNA by the reverse transcriptase-PCR (RT-PCR) or confirmatory detection
of HCV antibodies by serologic assays using recombinant HCV-specific antigens. In patients with reactive
HCV antibody screening test results but negative or undetectable HCV RNA test results, HCV antibody
confirmatory tests would be useful to distinguish between true- and false-reactive HCV antibody
screening test results. HCV antibodies are usually not detectable during the first 2 months following
infection, and they are usually detectable by the late convalescent stage (>6 months after onset) of
infection. These antibodies do not neutralize the virus, and they do not provide immunity against this
viral infection. Loss of HCV antibodies may occur in the years following resolution of infection.
Despite the value of serologic confirmation of HCV infection, several limitations of this test exist:
-There may be a long delay (up to 6 months) between exposure to the virus and development of
detectable HCV antibodies, especially in immunocompromised patients -A positive test result does not
distinguish between past (resolved) and chronic HCV infection -Serologic tests cannot predict or
monitor response to antiviral therapy See Hepatitis C: Testing Algorithm for Screening and Diagnosis in
Special Instructions.

**Useful For:** Confirming the presence of hepatitis C virus (HCV)-specific IgG antibodies in serum
specimens that are reactive by HCV antibody screening tests Distinguishing between true- and
false-reactive HCV antibody screening test results

**Interpretation:** A positive result indicates the presence of hepatitis C virus (HCV)-specific IgG
antibodies due to past (resolved) or chronic hepatitis C. Past (resolved) HCV infection (accounting for
about 25% of all HCV-infected patients) can be distinguished from chronic HCV infection (about 75% of all cases) only by direct detection of HCV RNA using molecular test methods; eg, HCVQN / Hepatitis C Virus (HCV) RNA Detection and Quantification by Real-Time Reverse Transcription-PCR (RT-PCR), Serum. HCV RNA is present in acute or chronic hepatitis C but not in past (resolved) HCV infection. A negative result indicates the absence of HCV-specific IgG antibodies. A reactive HCV antibody screening test result with a negative HCV antibody confirmatory result indicates a probable false-reactive screening test result. An indeterminate result indicates that HCV-specific IgG antibodies may or may not be present. Indeterminate results should be interpreted along with patient's risk factors for HCV infection and clinical findings. Individuals at risk for HCV infection with indeterminate results should be retested with an HCV antibody confirmatory test in 1 to 2 months to determine the definitive HCV antibody status. Molecular tests to detect HCV RNA may be necessary to determine HCV infection status in those at-risk immunocompromised patients with indeterminate HCV antibody confirmatory test results due to delayed appearance of fully complement of HCV-specific antibodies.

Reference Values:

Negative


HCCDD 58127

Hepatitis C Virus Antibody in Cadaveric or Hemolyzed Specimens, Serum

Clinical Information: Hepatitis C virus (HCV) is recognized as the cause of most cases of post-transfusion hepatitis and is a significant cause of morbidity and mortality worldwide. In the United States, HCV infection is quite common, with an estimated 3.5 to 4 million chronic HCV carriers. HCV antibodies are usually not detectable during the early months following infection, but they are almost always detectable by the late convalescent stage (>6 months after onset of acute infection). These antibodies do not neutralize the virus, and they do not provide immunity against this viral infection. Loss of HCV antibodies may occur many years following resolution of infection. Despite the value of serologic tests to screen for HCV infection, several limitations of serologic testing are known: -There may be a long delay (up to 6 months) between exposure to the virus and the development of detectable antibodies. -False-reactive screening test results can occur. -A reactive screening test result does not distinguish between past (resolved) and present HCV infection. -Serologic tests cannot provide information on clinical response to antiviral therapy. Positive screening serologic test results should be followed by a confirmatory or supplemental test, such as line immunoassay (HCVL) for HCV antibodies or a nucleic acid test for HCV RNA. Although nucleic acid tests provide a very sensitive and specific approach to directly detect HCV RNA in a patient's blood, they are not suitable for use in testing cadaveric or hemolyzed serum specimens due to interference of heme with the nucleic acid amplification processes.

Useful For: Diagnosis of hepatitis C virus (HCV) infection in cadaveric or hemolyzed serum specimens from symptomatic patients with or without risk factors for HCV infection Note: This test is not intended for screening blood, cell, or tissue donors. Not useful to rule-out acute HCV infection. Not useful for differentiation between resolved and acute or chronic hepatitis C infection.

Interpretation: All specimens with signal-to-cutoff ratios of 1.0 or greater will be considered reactive and reflexed to the hepatitis C virus (HCV) IgG antibody confirmatory test by line immunoassay (HCVL) at an additional charge. Additional testing is needed to differentiate between past (resolved) and chronic
hepatitis C. A negative screening test result does not exclude the possibility of exposure to or infection with HCV. Negative screening test results in individuals with prior exposure to HCV may be due to antibody levels below the limit of detection of this assay or lack of reactivity to the HCV antigens used in this assay. Patients with recent HCV infections (<3 months from time of exposure) may have false-negative HCV antibody results due to the time needed for seroconversion (average of 8 to 9 weeks).

Reference Values:
Negative

Clinical References:

HCCAD 87858

Hepatitis C Virus Antibody Screen for Cadaveric or Hemolyzed Specimens, Serum

Clinical Information: Hepatitis C virus (HCV) is recognized as the cause of most cases of post-transfusion hepatitis and is a significant cause of morbidity and mortality worldwide. In the United States, HCV infection is quite common, with an estimated 3.5 to 4 million chronic HCV carriers. HCV antibodies are usually not detectable during the early months following infection, but they are almost always detectable by the late convalescent stage (>6 months after onset of acute infection). These antibodies do not neutralize the virus, and they do not provide immunity against this viral infection. Loss of HCV antibodies may occur many years following resolution of infection. Despite the value of serologic tests to screen for HCV infection, several limitations of serologic testing are known: - There may be a long delay (up to 6 months) between exposure to the virus and the development of detectable antibodies. - False-reactive screening test results can occur. - A reactive screening test result does not distinguish between past (resolved) and present HCV infection. - Serologic tests cannot provide information on clinical response to antiviral therapy. Positive screening serologic test results should be followed by a confirmatory or supplemental test, such as line immunoassay for HCV antibodies or a nucleic acid test for HCV RNA. Although nucleic acid tests provide a very sensitive and specific approach to directly detect HCV RNA in a patient's blood, they are not suitable for use in testing cadaveric or hemolyzed serum specimens due to interference of heme with the nucleic acid amplification processes.

Useful For: Screening cadaveric or hemolyzed serum specimens for hepatitis C virus (HCV) infection in asymptomatic individuals with or without risk factors for HCV infection Note: In accordance with National Coverage Determination guidance, this test is indicated for asymptomatic patients born from 1945 through 1965, those with history of injection drug use, or history of receiving blood transfusion prior to 1992. Not useful rule-out acute HCV infection. Not useful for differentiation between resolved and acute or chronic HCV infection.

Interpretation: All specimens with signal-to-cutoff ratios of 1.0 or greater will be considered reactive and reflex to the hepatitis C virus (HCV) antibody confirmatory test by line immunoassay (HCV-L) at an additional charge. Additional testing is needed to differentiate between past (resolved) and chronic hepatitis C. A negative screening test result does not exclude the possibility of exposure to or infection with HCV. Negative screening test results in individuals with prior exposure to HCV may be due to antibody levels below the limit of detection of this assay or lack of reactivity to the HCV antigens used in this assay. Patients with recent HCV infections (<3 months from time of exposure) may have false-negative HCV antibody results due to the time needed for seroconversion (average of 8 to 9 weeks).

Reference Values:
Negative

Clinical References:
2. Centers for Disease Control and Prevention (CDC): Testing for

**HCVG 81618**

**Hepatitis C Virus Genotype, Serum**

**Clinical Information:** Unique nucleotide sequences of certain regions (eg, 5'-noncoding, core, NS5b) of the hepatitis C virus (HCV) genome allow classification of HCV into 6 major genotypes or clades (1-6), based on the most recently proposed HCV genotype nomenclature. In the United States, the most commonly encountered HCV genotypes are 1a and 1b, followed by genotypes 2 and 3. Worldwide geographic distribution, disease outcome, and response to antiviral therapy differ among the genotypes. Therefore, reliable methods for genotype determination are important for proper selection of antiviral therapy and optimal patient management. Infections with HCV genotypes 2 and 3 have better therapeutic response rates (80%-90%) than genotypes 1 and 4 (40%-50%) to previous standard combination therapy (ribavirin plus pegylated interferon alpha-2a or alpha-2b). Duration of such combination therapy is 24 weeks for chronic HCV genotype 2 and 3 infections in patients who show early virologic response (>2 log or 100-fold decrease in HCV RNA or no detectable HCV RNA at week 12 of therapy), while patients with chronic HCV genotype 1 and 4 infections receive a minimum of 48 weeks of such combination therapy if early virologic response is achieved (undetectable HCV RNA at week 4 of therapy). Therapeutic response rates for HCV genotype 1 infection are improved significantly (80%-90%) when oral direct acting antiviral agents (eg, simeprevir, sofosbuvir, ledipasvir + sofosbuvir, daclatasvir + sofosbuvir, omibitasvir + paritaprevir + ritonavir + dasabuvir) are added or used in lieu of interferon-based combination therapy. However, antiviral resistance can emerge during such combination therapy, and occurrence of such resistance is more frequent with HCV subtype 1a than 1b for simeprevir-treated patients. The American Association for the Study of Liver Diseases (AASLD) and Infectious Disease Society of America (IDSA) recommendations for testing, managing, and treating hepatitis C are available at www.hcvguidelines.org/full-report-view

**Useful For:** Determining hepatitis C virus genotype (1 to 5) to guide antiviral therapy in patients with chronic hepatitis C Differentiating between hepatitis C virus subtypes 1a and 1b

**Interpretation:** An "Undetected" result indicates the absence of detectable hepatitis C virus (HCV) RNA in the specimen. An "Indeterminate" result may be due to 1 or more of the following causes: 1) low HCV RNA level (ie, <500 IU/mL), 2) HCV genotype 6, 3) probe reactivity with multiple HCV genotypes, or 4) variation in patient's HCV target sequences with mismatches to PCR primers and/or probes. Specimens generating indeterminate results with this assay will be automatically evaluated with the subsequent test HCVGR / Hepatitis C Virus Genotype Resolution, Serum. An HCV genotype result of "1" without a subtype result may be due to 1 or more of the following causes: 1) low HCV RNA level (ie, <500 IU/mL), 2) probe reactivity with multiple genotype 1 subtypes, 3) variation in HCV genotype 1 target sequence, or 4) misclassification of some true genotype 6 strains. This assay is able to differentiate between HCV subtypes 1a and 1b. However, subtypes are not reported for HCV genotypes 2 to 5 due to limitations of the current genotyping assay in accurately differentiating the various subtypes of these genotypes. Results with multiple or mixed HCV genotypes (eg, 1, 5; 1a, 2; or 3, 5) may be due to mixed genotype infection or assay probe cross-reactivity. Only those specimens with multiple or mixed genotype results containing genotype 1 but no subtype will be automatically evaluated with the subsequent test HCVGR / Hepatitis C Virus Genotype Resolution, Serum.

**Reference Values:**

**Undetected**

Clinical Information: Of all individuals infected with hepatitis C virus (HCV), about 75% of them will develop chronic hepatitis C, with ongoing viral replication in the liver and detectable HCV RNA in serum or plasma, eventually resulting in cirrhosis. The remaining 25% of the infected individuals recover from the infection without evidence of viral replication or the presence of detectable HCV RNA in serum or plasma. Chronic HCV infection can be cured at variable success rates with either combined interferon-alpha and ribavirin therapy or interferon-free combination of direct-acting antiviral (DAA) agents. The antiviral response rates correlate with pretreatment serum or plasma HCV RNA levels (viral load) and the HCV genotype found in the infected individuals. The optimal duration of combined interferon and ribavirin therapy can be determined from the patient's pretreatment viral load and HCV genotype. Clinical trial studies indicated that a decrease in HCV RNA levels of more than 2 log IU/mL at 4 weeks or 12 weeks of therapy is predictive of an increased chance of achieving a sustained virologic response (defined as undetectable HCV RNA levels in serum 6 months after completing antiviral therapy). Despite receiving longer duration of antiviral therapy (48 weeks versus 24 weeks), patients with chronic infection due to HCV genotypes 1 and 4 generally have less favorable sustained virologic response rates (40%-50%) than those infected with genotypes 2 and 3 (>80%). Due to the necessary prolonged duration (typically 24 to 48 week duration) and low cure rates of such antiviral therapy, interferon-based therapy has been supplanted with potent interferon-free DAA combination therapy now. Unique nucleotide sequences of certain regions (eg, 5'-noncoding, core, NS5b) of the HCV genome allow classification of HCV into 6 major genotypes or clades (1-6), based on the most recently proposed HCV genotype nomenclature. In the United States, the most commonly encountered HCV genotypes are 1a and 1b, followed by genotypes 2 and 3. Worldwide geographic distribution, disease outcome, and response to antiviral therapy differ among the genotypes. HCV genotype determination is important for proper selection of antiviral therapy and optimal patient management. Therapeutic response rates for chronic HCV infection have improved significantly (cure rates of >90%) over the past 5 years when oral DAA agents are used in lieu of interferon-based combination therapy. However, antiviral resistance can emerge during such combination therapy, and occurrence of such resistance is more frequent with HCV subtype 1a than 1b for simprevir-treated patients. The American Association for the Study of Liver Diseases (AASLD) and Infectious Disease Society of America (IDSA) recommendations for testing, managing, and treating hepatitis C are available at www.hcvguidelines.org/full-report-view.

Useful For: Detection of acute HCV infection before the appearance of HCV antibodies in serum (ie, <2 months from exposure) Detection and confirmation of chronic HCV infection, and determining HCV genotype (1 to 5) to guide antiviral therapy in patients with chronic hepatitis C Quantification of HCV RNA in serum of patients with chronic HCV infection (HCV antibody-positive) before initiating antiviral therapy Determining cure and detection of relapse of HCV infection after completion of antiviral therapy

Interpretation: This assay has a result range of 15 to 100,000,000 IU/mL (1.18 log to 8.00 log IU/mL) for quantification of hepatitis C virus (HCV) RNA in serum. Only those specimens with HCV RNA levels of greater than or equal to 500 IU/mL will be tested for HCV genotype (HCVG / Hepatitis C Virus Genotype, Serum or HCVGR / Hepatitis C Virus Genotype Resolution, Serum). An "Undetected" result indicates that the HCV is absent in the patient's serum specimen. Such specimens will not be tested for HCV genotype. A result of "<15 IU/mL (<1.18 log IU/mL)" indicates that HCV RNA is detected, but the HCV RNA level present cannot be quantified accurately below this lower limit of quantification of this assay. Such specimens will not be tested for HCV genotype. A result of ">100,000,000 IU/mL (>8.00 log IU/mL)" indicates the presence of active HCV viral replication, and the HCV RNA level present cannot be quantified accurately above this upper limit of quantification of this assay. An "Inconclusive" result reported with a comment indicates that testing failed, likely due to presence of inhibitory substances in the submitted serum specimen. A new specimen should be collected for retesting. Such specimens will not be tested for HCV genotype.

Reference Values:
Hepatitis D Virus Total Antibodies, Serum

**Clinical Information:** Hepatitis D virus (HDV), also known as delta hepatitis virus, is a defective RNA virus comprised of a delta antigen and a hepatitis B surface antigen (HBsAg) as the core and protein coat of the virus, respectively. This virus cannot replicate effectively by itself, and it requires the presence of hepatitis B virus (HBV) to initiate and maintain its replication in the infected liver cells. Infection with HDV occurs either as an acute coinfection with HBV or an acute superinfection of chronic HBV. Acute HBV-HDV coinfection usually follows a self-limited clinical course with spontaneous resolution, but may have a fulminant clinical presentation. HDV superinfection in chronic HBV or in HBV carrier state typically manifests as an acute exacerbation of chronic hepatitis B, with tendency to result in chronic HBV-HDV coinfection and early cirrhosis or liver failure. Chronic HDV infection is found in 1% of all chronically HBV-infected individuals in the United States. Diagnosis of HDV can be established by detecting HDV antigen, HDV-specific IgM, or HDV-specific total antibodies (combined IgM and IgG) in the sera of infected patients with clinically evident acute or chronic hepatitis B. Anti-HDV IgM typically appears in serum at 2 to 3 weeks after onset of symptoms and disappears by 2 months after acute HDV infection, but it may persist up to 9 months in HDV superinfection. HDV IgG and HDV total antibodies persist in serum after resolution of acute HDV infection and in chronic coinfection.

**Useful For:** Detection of hepatitis D virus (HDV)-specific total antibodies (combined IgG and IgM) in human serum Diagnosis of concurrent HDV infection in patients with acute hepatitis B virus (HBV) infection (acute coinfection), chronic HBV infection (chronic coinfection), or acute exacerbation of known chronic HBV infection (HDV superinfection)

**Interpretation:** This assay detects the presence of hepatitis D virus (HDV)-specific total (combined IgG and IgM) antibodies in serum. Negative results indicate the absence of HDV infection and no past exposure to HDV. Equivocal results indicate borderline level of anti-HDV total antibodies. Repeat testing in 1 to 2 weeks is recommended to determine the definitive HDV infection status. Positive results usually indicate 1 of the following conditions: 1) simultaneous acute or chronic coinfection with hepatitis B virus (HBV) and HDV, 2) acute HDV infection in patients with known chronic HBV infection (ie, HDV superinfection), or 3) resolved HDV infection. See Viral Hepatitis Serologic Profiles in Special Instructions.

**Reference Values:**
Negative

**Clinical References:**
parenterally, and direct person-to-person transmission is rare. Clinically severe cases occur in young to middle-aged adults. Unusually high mortality (approximately 20%) occurs in patients infected during the third trimester of pregnancy. Although there is no carrier state associated with HEV, immunocompromised patients may have prolonged periods (eg, months) of viremia and virus shedding in the stool. In immunocompetent patients, viremia and virus shedding in the stool occur in the preicteric phase, lasting up to 10 days into the clinical phase. After an incubation period ranging from 15 to 60 days, HEV-infected patients develop symptoms of hepatitis with appearance of anti-HEV IgM antibody in serum, followed by detectable anti-HEV IgG within a few days. Anti-HEV IgM may remain detectable up to 6 months after onset of symptoms, while anti-HEV IgG usually persists for many years after infection. Anti-HEV IgG is the serologic test of choice to determine past exposure to HEV.

Useful For: Diagnosis of past exposure to hepatitis E virus

Interpretation: Positive results indicate past or resolved hepatitis E infection. Negative results indicate absence of previous exposure to hepatitis E virus (HEV). Borderline results may be seen in: 1) acute or recent hepatitis E infection with rising level of anti-HEV IgG, or 2) cross-reactivity with nonspecific antibodies (ie, false-positive results). Repeat testing of serum for anti-HEV IgG in 4 to 6 weeks is recommended to determine the definitive HEV infection status.

Reference Values: Negative


Hepatitis E Virus IgM Antibody Confirmation, Serum

Clinical Information: Hepatitis E virus (HEV) causes an acute, usually self-limited infection. This small, nonenveloped RNA virus is from animal reservoirs (eg, hogs) and is transmitted to humans via the fecal-oral route. HEV is endemic in Southeast and Central Asia, with several outbreaks observed in the Middle East, northern and western parts of Africa, and Mexico. In developed countries, HEV infection occurs mainly in persons who have traveled to disease-endemic areas. Transmission of HEV may also occur parenterally, and direct person-to-person transmission is rare. Clinically severe cases occur in young to middle-aged adults. Unusually high mortality (approximately 20%) occurs in patients infected during the third trimester of pregnancy. Although there is no carrier state associated with HEV, immunocompromised patients may have prolonged periods (eg, months) of viremia and virus shedding in the stool. In immunocompetent patients, viremia and virus shedding in the stool occur in the preicteric phase, lasting up to 10 days into the clinical phase. After an incubation period ranging from 15 to 60 days, HEV-infected patients develop symptoms of hepatitis with appearance of anti-HEV IgM antibody in serum, followed by detectable anti-HEV IgG within a few days. Anti-HEV IgM may remain detectable up to 6 months after onset of symptoms, while anti-HEV IgG usually persists for many years after infection. Anti-HEV IgM is the serologic marker of choice for diagnosis of acute HEV infection. Positive predictive value of a given diagnostic laboratory test is dependent on the prevalence rate of the disease for which the test is being used. Screening tests for detection of diseases with low prevalence rates, such as acute hepatitis E, will have low positive predictive values (ie, relatively high rates of false-positive test results), despite having high specificity rates for such tests. Therefore, an HEV IgM antibody confirmatory test is helpful and necessary to determine the true infection status of patients with reactive HEV IgM antibody screening test results.

Useful For: Confirmation of reactive hepatitis E virus IgM antibody screening test results for the diagnosis of acute or recent (<6 months) hepatitis E infection

Interpretation: Positive results confirm the presence of acute or recent (in the preceding 6 months) hepatitis E infection. Negative results indicate absence of acute or recent hepatitis E infection. Indeterminate results may be seen in: 1) acute hepatitis E infection with rising level of anti-hepatitis E virus (HEV) IgM; 2) recent hepatitis E infection with declining level of anti-HEV IgM; 3) acute hepatitis E infection due to HEV genotype 2 strains; or 4) cross-reactivity with nonspecific antibodies.
(ie, false-positive results). Repeat testing of serum for anti-HEV IgM and anti-HEV IgG in 4 to 6 weeks is recommended to determine the definitive HEV infection status. Unreadable results indicate the presence of unusually strong, nonspecific reactivity of the assay strip background that obscures proper reading of the bands. Such findings are usually due to nonspecific binding of non-hepatitis E IgM antibodies in patient's serum to the HEV antigens present on the assay strip. Repeat testing with anti-HEV IgM screen and anti-HEV IgG in 1 to 2 weeks is recommended.

**Reference Values:**

Negative

**Clinical References:**


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**HEVQU**

**Hepatitis E Virus RNA Detection and Quantification by Real-Time RT-PCR, Serum**

**Clinical Information:** Hepatitis E virus (HEV) is a causative agent of acute self-limited or fulminant hepatitis. HEV has been responsible for large outbreaks of disease in developing countries, primarily through waterborne transmission. Hepatitis E also can occur in industrialized countries, usually as
sporadic cases due to zoonotic infection transmitted by the fecal-oral route. A major natural reservoir of HEV is pigs. In immunocompetent individuals, hepatitis E is mainly a self-limited infection, frequently non-symptomatic and does not result in chronic infection. However, in otherwise healthy pregnant patients, hepatitis E can be severe resulting in significant morbidity and mortality. In immunocompromised individuals, such as organ transplant recipients, hepatitis E can be chronic with detectable HEV RNA levels in serum and plasma beyond 3 months after infection. HEV-specific IgM antibody is detectable by serologic testing by 4 weeks after infection in immunocompetent individuals, but it may not be detectable until 6 months after infection in immunosuppressed patients. HEV RNA levels in serum or plasma are usually detectable in all infected individuals by 3 weeks after infection and become undetectable by 7 weeks in immunocompetent individuals. Due to the limitations of HEV serologic testing in immunosuppressed patients, molecular testing (eg, RT-PCR assay) for HEV RNA in serum or plasma is an increasingly important tool in the diagnosis of acute or chronic HEV infection in these patients. Currently, ribavirin is used as the antiviral agent of choice for organ transplant recipients with chronic HEV, and monitoring of HEV RNA levels in serum or plasma is used to assess response to such antiviral therapy. Significant decreases in HEV viral load or clearance of HEV RNA may be important predictors of virologic response during antiviral therapy.

**Useful For:** Virologic detection and confirmation of hepatitis E virus (HEV) infection in immunocompromised individuals at risk for or suspected to have acute or chronic hepatitis E Monitoring HEV RNA levels and determining eradication of chronic HEV infection in immunocompromised individuals

**Interpretation:** The quantification range of this assay is 100 to 5,000,000 IU/mL (2.00 log to 6.70 log IU/mL), with a limit of detection (based on a 95% detection rate) of 11 IU/mL (1.04 log IU/mL). An "Undetected" result indicates that hepatitis E virus (HEV) RNA is not detected in the serum specimen (see Cautions). Repeat testing in 1 to 2 months is recommended for those at risk of HEV infection. The limit of detection (based on a 95% detection rate) for this assay is 11 IU/mL. A result of "<100 IU/mL" indicates that the HEV RNA level present in the serum specimen is below 100 IU/mL (2.00 log IU/mL), and the assay cannot accurately quantify the HEV RNA present below this level. A quantitative value (reported in IU/mL and log IU/mL) indicates the HEV RNA level (ie, viral load) present in the serum specimen. A result of ">5,000,000 IU/mL," indicates that the HEV RNA level present in the serum specimen is above 5,000,000 IU/mL (6.70 log IU/mL), and this assay cannot accurately quantify the HEV RNA present above this level. An "Indeterminate" result suggests the presence of an atypical HEV target sequence. Since the HEV RNA sequence is atypical, repeat testing is unlikely to change this result and therefore is not recommended. An "Equivocal" result indicates that the presence or absence of HEV RNA in the serum specimen could not be determined with certainty due to atypical RT-PCR probe reactivity. Submission of a new specimen for testing is recommended. An "Inconclusive" result indicates that the presence or absence of HEV RNA in the serum specimen could not be determined with certainty after repeat testing in the laboratory, possibly due to RT-PCR inhibition. Submission of a new specimen for testing is recommended.

**Reference Values:**
Undetected

**Clinical References:**

**Hepatocellular Carcinoma Risk Panel**

**Clinical Information:** Worldwide, hepatocellular carcinoma is the third leading cause of death from cancer. (1) While hepatocellular carcinoma can be treated effectively in its early stages, most patients are not diagnosed until they are symptomatic and at higher grades and stages, which are less
responsive to therapies. Alpha-fetoprotein (AFP) is the standard serum tumor marker utilized in the evaluation of suspected hepatocellular carcinoma. However, increased serum concentrations of AFP might be found in chronic hepatitis and liver cirrhosis, as well as in other tumor types (eg, germ cell tumors[2]), decreasing the specificity of AFP testing for hepatocellular carcinoma. Furthermore, AFP is not expressed at high levels in all hepatocellular carcinoma patients, resulting in decreased sensitivity, especially in potentially curable small tumors. L3AFP: AFP is differentially glycosylated in several hepatic diseases. For example, UDP-alpha-1-->6-fucosyltransferase is differentially expressed in hepatocytes following malignant transformation.(3) This enzyme incorporates fucose residues on the carbohydrate chains of AFP. Different glycosylated forms of AFP can be recognized following lectophoresis by reaction with different carbohydrate-binding plant lectins. The fucosylated form of serum AFP that is most closely associated with hepatocellular carcinoma is recognized by a lectin from the common lentil (Lens culinaris). This is designated as AFP-L3 (third electrophoretic form of lentil lectin-reactive AFP). AFP-L3 is most useful in the differential diagnosis of individuals with total serum AFP < or =200 ng/mL, which may result from a variety of benign pathologies, such as chronic liver diseases. DCP: Des-gamma-carboxy prothrombin (DCP), also known as the protein induced by vitamin K absence or antagonist II (PIVKA-II), is an abnormal form of the coagulation protein, prothrombin. DCP is a nonfunctional prothrombin resulting from a lack of carboxylation of 10 glutamic acid residues in the N-terminal portion of the molecule. In normal liver, prothrombin undergoes post-translational carboxylation before release into the peripheral blood. The carboxylation converts specific amino-terminal glutamic acid residues to gamma-carboxyglutamic acid. The vitamin K dependent carboxylase responsible for the carboxylation is absent in many hepatocellular carcinoma (HCC) cells, and an abnormal prothrombin with all or some of unconverted glutamic acid is secreted. Therefore, this noncarboxylated form (DCP) has been used as an HCC biomarker. DCP is considered a complementary biomarker to alpha fetoprotein AFP and AFP-L3% for assessing the risk of developing HCC. The elevation of both AFP-L3% and DCP indicate progression of HCC, albeit they reflect different features of the progression. In a prospective study of patients in the United States with an established diagnosis of HCC, the sensitivities for AFP, AFP-L3%, and DCP were 68%, 62%, and 73%, respectively. When the 3 markers were combined, the sensitivity was 86%. In another study, DCP levels were shown to correlate with tumor size and metastatic HCC. In this study, compared to AFP and AFP-L3%, DCP had the highest sensitivity (87%) and the highest positive predictive value (87%) in patients with HCC due to chronic hepatitis B and C infections. A number of studies have shown that elevated serum DCP is significantly related to portal vein invasion and/or intrahepatic metastasis, which significantly affect prognosis for patients with HCC. DCP can be elevated in other conditions besides HCC. Conditions such as obstructive jaundice, intrahepatic cholestasis causing chronic decrease in vitamin K, and ingestion of drugs such as warfarin or wide-spectrum antibiotics can result in high concentrations of DCP. In addition, 25% to 50% of patients with HCC will have a DCP value within the reference range. Because of this, a normal DCP value does not rule out HCC.

**Useful For:** Risk assessment of patients with chronic liver disease for development of hepatocellular carcinoma

**Interpretation:** L3AFP: Alpha-fetoprotein (AFP)-L3 > or =10% is associated with a 7-fold increased risk of developing hepatocellular carcinoma. Patients with AFP-L3 > or =10% should be monitored more intensely for evidence of hepatocellular carcinoma according to current practice guidelines. Total serum AFP >200 ng/mL is highly suggestive of a diagnosis of hepatocellular carcinoma. In patients with liver disease, a total serum AFP of >200 ng/mL is near 100% predictive of hepatocellular carcinoma. With decreasing total AFP levels, there is an increased likelihood that chronic liver disease, rather than hepatocellular carcinoma, is responsible for the AFP elevation. Based on a retrospective study at Mayo Clinic, for patients with total AFP levels < or =200 ng/mL, AFP-L3 specificity approaches 100% for hepatocellular carcinoma when its percentage exceeds 35% of the total AFP.(4) AFP concentrations over 100,000 ng/mL have been reported in normal newborns, and the values rapidly decline in the first 6 years of life. DCP: In patients with an elevated des-gamma-carboxy prothrombin (DCP) result (> or =7.5 ng/mL), the risk of developing hepatocellular carcinoma (HCC) is 36.5% (95% CI 23.5%-49.6%). The risk of developing HCC with a negative DCP result (<7.5 ng/mL) is 7.6% (95% CI 4.4%-10.8%).

**Reference Values:**
- L3AFP: <10%
- DCP: <7.5 ng/mL

**HEPAT 70456**

**Hepatocyte (HEP) Immunostain, Technical Component Only**

**Clinical Information:** Normal liver tissue is positive with a distinct granular cytoplasmic staining of hepatocytes. Bile ducts and nonparenchymal liver cells are negative.

**Useful For:** Aids in distinguishing hepatocellular carcinoma from other types of cancer

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**HNF1B 70461**

**Hepatocyte Nuclear Factor 1Beta (HNF-1beta) Immunostain, Technical Component Only**

**Clinical Information:** Hepatocyte nuclear factor-1beta (HNF-1beta) is a transcription factor that regulates the transcription of the TCF2 gene into proteins. HNF-1beta has been shown to be upregulated in ovarian clear cell carcinoma.

**Useful For:** Aids in the diagnosis of ovarian clear cell carcinoma and endometrial clear cell carcinoma

**Interpretation:** This test includes only technical performance of the stain (no pathologist
interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**FHER 91518**

**HER-2/neu, Quantitative, ELISA**

**Reference Values:**
Reference Range: 0.0 - 15.0 ng/mL

Note: Graph attached as a supplemental report in MayoAccess

Test Performed By: LabCorp Burlington
1447 York Court
Burlington, NC 27215-2230

**Clinical References:**

**HER2F 35275**

**HER2 Amplification Associated with Breast Cancer, FISH, Tissue**

**Clinical Information:** HER2 (ERBB2: c-erb-b2) is an oncogene on the long arm of chromosome 17 that is amplified in approximately 15% to 20% of breast cancers. Amplification or overexpression of HER2 has been shown to be associated with shorter disease-free survival and poorer overall survival in breast cancer. Patients with HER2 gene amplification or overexpression are candidates for treatment with the drugs that target the human epidermal growth factor receptor 2 (HER2) protein and its downstream pathways (eg, trastuzumab [Herceptin], pertuzumab). FISH with labeled DNA probes to the pericentromeric region of chromosome 17 and to the HER2 locus can be used to determine if a patient's breast cancer has HER2 gene amplification. Immunohistochemical analysis is used to determine if a tumor exhibits HER2 overexpression.

**Useful For:** A predictive marker for patients with both node-positive or node-negative primary and metastatic breast cancer Confirming the presence of HER2 amplification in cases with 2+ (low level) or 3+ (high level) HER2 overexpression by immunohistochemistry, and for certain histologic subtypes with aberrant patterns of HER2 expression seen by immunohistochemistry (eg, micropapillary carcinoma)
**Interpretation:** An interpretive report is provided. Results are interpreted utilizing current American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines. Under the 2018 Focused Update to the ASCO/CAP Guidelines, reflex immunohistochemistry is performed for certain categories of results, known as Groups 2, 3, and 4. These categories are shown in the table below (Group 4 is the category formerly referred to as FISH "equivocal"). If reflex immunohistochemistry is performed and is either negative (0, 1+) or positive (3+), the result of the FISH assay is considered resolved by immunohistochemistry as either negative or positive. If the immunohistochemistry assay shows an equivocal (2+) result, then the FISH slide is rescored within the areas showing the most intense membranous (2+) staining and the final FISH result is used to determine whether the result is negative or positive. ASCO/CAP Result Category HER2:D17Z1 ratio; average HER2 copies per cell Reporting approach per 2018 ASCO/CAP guidelines Group 1 HER2:D17Z1 > or =2.00; HER2/cell > or =4.0 Positive Group 2 HER2:D17Z1 > or =2.00; HER2/cell <4.0 Reflex immunohistochemistry; FISH reanalysis if 2+ Group 3 HER2:D17Z1<2.00; HER2/cell > or > or =6.0 Reflex immunohistochemistry; FISH reanalysis if 2+ Group 4 HER2:D17Z1<2.00; HER2/cell > or > or =4.0 <6.0 Reflex immunohistochemistry; FISH reanalysis if 2+ Group 5 HER2:D17Z1<2.00; HER2/cell <4.0 Negative The degree of HER2 amplification varies in tumors. Some exhibit high levels of amplification (HER2:D17Z1 ratio >4.0), whereas others exhibit low-level amplification (HER2:D17Z1 ratio of 2.0-4.0). It is not currently known if patients with different levels of amplification have the same prognosis and response to therapy. Reports also interpret the HER2 copy number changes relative to chromosome 17 copy number (aneusomy) or potential structural genomic abnormalities that increase HER2 copy number. Rare cases may not show HER2 amplification but still have human epidermal growth factor receptor 2 (HER2) protein overexpression demonstrated by immunohistochemistry. The clinical significance of HER2 protein overexpression in the absence of HER2 gene amplification is unclear. However, these patients may have a worse prognosis and be candidates for treatments that target the HER2 protein or its downstream pathways.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**H2GEF 35273**

**HER2 Amplification Associated with Gastroesophageal Cancer, FISH, Tissue**

**Clinical Information:** Gastroesophageal cancer is one of the most commonly diagnosed cancers. To date, chemotherapy for gastroesophageal cancer is often ineffective and its prognosis remains poor. Recent studies suggest that the HER2 oncogene can be used as a marker to identify aggressive disease. In much the same way as was demonstrated for HER2-positive breast cancer, the HER2 gene status in gastroesophageal cancers can be used to determine treatment approaches. Amplification of the HER2
gene and overexpression of the human epidermal growth factor receptor 2 (HER2) protein have been associated with a shorter disease-free survival and shorter overall survival in gastric and gastroesophageal junction cancers. Patients whose tumors demonstrate HER2 amplification or overexpression may be candidates for treatment with the drugs that target the HER2 protein or its downstream pathways (e.g., trastuzumab [Herceptin], pertuzumab).

**Useful For:** Guiding therapy for patients with primary or metastatic gastroesophageal tumors, as patients with HER2 amplification may be candidates for therapies that target the human epidermal growth factor receptor 2 (HER2) protein (e.g., trastuzumab [Herceptin], pertuzumab) Confirming the presence or absence of HER2 amplification in cases with 2+ (equivocal) HER2 overexpression by immunohistochemistry

**Interpretation:** An interpretive report is provided. Results are interpreted utilizing the 2016 College of American Pathologists (CAP)/American Society for Clinical Pathology (ASCP)/American Society of Clinical Oncology (ASCO) guidelines for gastric tumors, and the guidelines used by the ToGA trial. Specimens with equivocal results as defined by 2016 CAP/ASCP/ASCO guidelines will no longer have reflex testing performed using an alternative FISH probe set. The report will include a complete interpretation including the HER2:D17Z1 results. The degree of HER2 amplification varies in tumors. Some exhibit high levels of amplification (HER2:D17Z1 ratio >4.0), whereas others exhibit low-level amplification (HER2:D17Z1 ratio of 2.0-4.0). It is not currently known if patients with different levels of amplification have the same prognosis or response to therapy. Reports also interpret the HER2 copy number changes relative to chromosome 17 copy number (aneusomy) or potential structural genomic abnormalities that increase HER2 copy number. Rare cases may not show HER2 amplification but still have human epidermal growth factor receptor 2 (HER2) protein overexpression demonstrated by immunohistochemistry. The clinical significance of HER2 protein overexpression in the absence of HER2 gene amplification is unclear. However, these patients may have a worse prognosis and be candidates for treatments that target the HER2 protein or its downstream pathways.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

**HER2 Amplification Associated with Urothelial Carcinoma, FISH, Tissue**

**Clinical Information:** Human epidermal growth factor receptor 2 (HER2) plays a fundamental role in cell growth, survival, and migration. The assessment of HER2 gene status is crucial for the management of breast cancer. Studies have shown that HER2 is also expressed in a proportion of urothelial carcinoma of the urinary bladder (UCB), making it a potential target for UCB therapy. HER2-positive gene status is associated with aggressive UCB and provides independent prognostic information. Assessment of HER2 status may be used to identify patients at high risk of disease progression.

**Useful For:** Guiding therapy for patients with primary or metastatic urothelial tumors, as patients with HER2 amplification may be candidates for therapies that target the human epidermal growth factor receptor 2 (HER2) protein (e.g., trastuzumab [Herceptin], pertuzumab) Confirming the presence of HER2
amplification in cases with 2+ (low level) or 3+ (high level) HER2 protein overexpression by immunohistochemistry, and for certain histologic subtypes with aberrant patterns of HER2 expression seen by immunohistochemistry (eg, micropapillary carcinoma)

**Interpretation:** An interpretive report is provided. Results are interpreted utilizing the 2013 American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines for breast tumors. Specimens with equivocal (Group 4) results as defined by 2013 ASCO/CAP guidelines will no longer have reflex testing performed using an alternative FISH probe set. The report will include a complete interpretation including the HER2:D17Z1 results. The degree of HER2 amplification varies in tumors. Some exhibit high levels of amplification (HER2:D17Z1 ratio >4.0), whereas others exhibit low-level amplification (HER2:D17Z1 ratio of 2.0-4.0). It is not currently known if patients with different levels of amplification have the same prognosis and response to therapy. Reports also interpret the HER2 copy number changes relative to chromosome 17 copy number (aneusomy) or potential structural genomic abnormalities that increase HER2 copy number. Rare cases may not show HER2 amplification but still have human epidermal growth factor receptor 2 (HER2) protein overexpression demonstrated by immunohistochemistry. The clinical significance of HER2 protein overexpression in the absence of HER2 gene amplification is unclear. However, these patients may have a worse prognosis and be candidates for treatments that target the HER2 protein or its downstream pathways.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

**HER2 Amplification, Miscellaneous Tumor, FISH, Tissue**

**Clinical Information:** Amplification of the HER2 oncogene and overexpression of the human epidermal growth factor receptor 2 (HER2) protein have been associated with a shorter disease-free survival and shorter overall survival and poorer overall survival in some cancers. Patients whose breast or gastroesophageal cancers demonstrate HER2 amplification or overexpression may be candidates for treatment with the drugs that target the HER2 protein or its downstream pathways (eg, trastuzumab [Herceptin], pertuzumab, lapatinib).

**Useful For:** Guiding cancer therapy, as patients with HER2 amplification may be candidates for therapies that target the human epidermal growth factor receptor 2 (HER2) protein (eg, trastuzumab [Herceptin], pertuzumab, lapatinib) Confirming the presence of HER2 amplification in cases with 2+ (low level) or 3+ (high level) HER2 protein overexpression by immunohistochemistry

**Interpretation:** An interpretive report is provided. Results are interpreted utilizing the 2013 American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines for breast tumors. Specimens with equivocal (Group 4) results as defined by 2013 ASCO/CAP guidelines will no longer have reflex testing performed using an alternative FISH probe set. The report will include a complete interpretation including the HER2:D17Z1 results. The degree of HER2 amplification varies in tumors. Some exhibit a high level of amplification (HER2:D17Z1 ratio >4.0), whereas others exhibit low-level amplification (HER2:D17Z1 ratio of 2.0-4.0). It is not currently known if patients with different levels of amplification have a similar prognosis or response to therapy. Reports also interpret the HER2 copy number changes relative to chromosome 17 copy number (aneusomy) or
potential structural genomic abnormalities that increase HER2 copy number. Rare cases may not show HER2 amplification but have human epidermal growth factor receptor 2 (HER2) protein overexpression demonstrated by immunohistochemistry. The clinical significance of HER2 protein overexpression in the absence of HER2 gene amplification is unclear. However, these patients may have a worse prognosis and may be candidates for treatments that target the HER2 protein or its downstream pathways.

Reference Values:
An interpretative report will be provided.


HER2 Immunostain, Without Interpretation

Clinical Information: The human HER2 gene (also known as ERBB2 or NEU) encodes a protein often referred to as HER2 protein or P185(HER2). The HER2 protein is a membrane receptor tyrosine kinase with homology to the epidermal growth factor receptor (EGFR or HER1). The HER2 protein is a normal component expressed by a variety of epithelial cell types.

Useful For: Identification of HER2 protein overexpression in formalin-fixed, paraffin-embedded tissue sections

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**HER2, Breast, DCIS, Quantitative Immunohistochemistry, Manual No Reflex**

**Clinical Information:** The HER2 (official gene name ERBB2) proto-oncogene encodes a membrane receptor with tyrosine kinase activity and homology to the epidermal growth factor receptor. Amplification and overexpression of the HER2 gene in human breast, endometrial, ovarian, and other epithelial cancers have been associated with a shorter disease-free interval and shorter overall survival. Overexpression of HER2 protein is an indication for Herceptin therapy in patients with breast cancer.

**Useful For:** Determining overexpression of HER2 protein on formalin-fixed, paraffin-embedded tissue sections in ductal carcinoma in situ or solid/intracystic papillary carcinoma breast tissue. This FDA-approved test is most frequently used to evaluate HER2 overexpression in breast cancer.

**Interpretation:** Results are reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody.

**Reference Values:**
Reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody.

**Clinical References:**

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**HER2, Breast, DCIS, Quantitative Immunohistochemistry, Manual with HER2 FISH Reflex**

**Clinical Information:** The HER2 (official gene name ERBB2) proto-oncogene encodes a membrane receptor with tyrosine kinase activity and homology to the epidermal growth factor receptor. Amplification and overexpression of the HER2 gene in human breast, endometrial, ovarian, and other epithelial cancers have been associated with a shorter disease-free interval and shorter overall survival. Overexpression of HER2 protein is an indication for Herceptin therapy in patients with breast cancer.

**Useful For:** Determining overexpression of HER2 protein on formalin-fixed, paraffin-embedded tissue sections in ductal carcinoma in situ or solid/intracystic papillary carcinoma breast tissue with a reflex to FISH testing if the specimen is equivocal (2+)

**Interpretation:** Results are reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody.

**Reference Values:**
Reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody.

**Clinical References:**
HER2, Breast, Quantitative Immunohistochemistry, Automated with HER2 FISH Reflex

Clinical Information: The HER2 (official gene name ERBB2) proto-oncogene encodes a membrane receptor with tyrosine kinase activity and homology to the epidermal growth factor receptor. Amplification and overexpression of the HER2 gene in human breast, endometrial, ovarian, and other epithelial cancers have been associated with a shorter disease-free interval and shorter overall survival. Overexpression of HER2 protein is an indication for Herceptin therapy in patients with breast cancer. This FDA-approved test is most frequently used to evaluate HER2 overexpression in breast cancer.

Useful For: Determining overexpression of HER2 protein on formalin-fixed, paraffin-embedded tissue sections using automated quantitative immunohistochemistry

Interpretation: Results are reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody. The scoring method using the Aperio digital pathology system was developed and validated in the Molecular Anatomic Pathology Laboratory, Department of Laboratory Medicine and Pathology, Mayo Clinic (see Method Description).

Reference Values: Reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody.


HER2, Breast, Quantitative Immunohistochemistry, Automated, No Reflex

Clinical Information: The HER2 (official gene name ERBB2) proto-oncogene encodes a membrane receptor with tyrosine kinase activity and homology to the epidermal growth factor receptor. Amplification and overexpression of the HER2 gene in human breast, endometrial, ovarian, and other epithelial cancers have been associated with a shorter disease-free interval and shorter overall survival. Overexpression of HER2 protein is an indication for Herceptin therapy in patients with breast cancer.

Useful For: Determining overexpression of HER2 protein on formalin-fixed, paraffin-embedded tissue sections without a reflex to FISH testing. This FDA-approved test is most frequently used to evaluate HER2 overexpression in breast cancer.

Interpretation: Results are reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody. The scoring method using the Aperio digital pathology system was developed and validated in the Molecular Anatomic Pathology Laboratory, Department of Laboratory Medicine and Pathology, Mayo Clinic (see Method Description).

Reference Values: Reported as negative (0, 1+), equivocal (2+), and strongly positive (3+) according to the interpretation guidelines for the FDA-approved Ventana Pathway HER2 (4B5) antibody.
**HERGM 70911**

**HER2, Gastric/Esophageal, Semi-Quantitative Immunohistochemistry, Manual**

**Clinical Information:** The HER2 (official gene name ERBB2) proto-oncogene encodes a membrane receptor with tyrosine kinase activity and homology to the epidermal growth factor receptor. Amplification and overexpression of the HER2 gene have been associated with a shorter disease-free survival and shorter overall survival in gastric and gastroesophageal junction cancers, as well as breast, endometrial, and ovarian cancer.(1,2)

**Useful For:** Determining overexpression of HER2 protein of gastric and esophageal adenocarcinoma in formalin-fixed, paraffin-embedded tissue sections (with reflex to FISH testing)

**Interpretation:** Results are reported as positive (3+ HER2 protein expression), equivocal (2+), or negative (0 or 1+). Equivocal (2+) cases will automatically reflex to FISH testing at an additional charge.

**Reference Values:**
Reported as negative (0, 1+), equivocal (2+), and positive (3+)


**HERGN 70914**

**HER2, Gastric/Esophageal, Semi-Quantitative Immunohistochemistry, Manual, No Reflex**

**Clinical Information:** The HER2 (official gene name ERBB2) proto-oncogene encodes a membrane receptor with tyrosine kinase activity and homology to the epidermal growth factor receptor. Amplification and overexpression of the HER2 gene have been associated with a shorter disease-free survival and shorter overall survival in gastric and gastroesophageal junction cancers, as well as breast, endometrial, and ovarian cancer.(1,2)

**Useful For:** Determining overexpression of HER2 protein of gastric and esophageal adenocarcinoma in formalin-fixed, paraffin-embedded tissue sections (no reflex to FISH testing)

**Interpretation:** Results are reported as positive (3+ HER2 protein expression), equivocal (2+), or negative (0 or 1+)

**Reference Values:**
Reported as negative (0, 1+), equivocal (2+), and positive (3+)

**Hereditary Breast and Colorectal Cancer Panel**

**Clinical Information:** While the risk for breast and colorectal cancer in the general population is 12% and 6%, respectively, these cancers are rarely attributable to a single abnormal gene that predisposes individuals to increased risks for cancer in a family. Given the prevalence of breast and colon cancer in the general population, it can be challenging to evaluate families with both breast and colon cancer for a possible hereditary predisposition. This panel allows for evaluation of the most common genes associated with both hereditary breast and hereditary colon cancer. Additionally, there is recent evidence to suggest an increased risk for breast cancer associated with the genes that cause Lynch syndrome. Therefore, evaluation for the genes on this panel may be useful for families suspicious of either a hereditary predisposition to breast cancer, colorectal cancer or both. Hereditary Breast and Ovarian Cancer Hereditary breast and ovarian cancer (HBOC) is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the BRCA1 or BRCA2 genes. Mutations within these 2 genes account for the majority of hereditary breast and ovarian cancer families. HBOC is predominantly characterized by young-onset breast cancer and ovarian cancer. However, HBOC is also associated with increased risks for prostate cancer, pancreatic cancer, fallopian tube cancer, and male breast cancer. HBOC is highly penetrant; the risk for developing an invasive breast cancer is about 60% to 65% and the risk for developing ovarian cancer is about 40% by age 70. Some individuals develop multiple primary or bilateral cancers. Hereditary Breast Cancer While pathogenic BRCA1 and BRCA2 variants account for the majority of hereditary breast cancer, mutations in other genes may be present in families in which a BRCA1 or BRCA2 gene mutation is not identified. These include TP53, PTEN, CDH1, and STK11. For instance, it has been demonstrated that 8% of women with very early-onset (less than 30 years of age) breast cancer who test negative for a mutation in BRCA1 and BRCA2 have a mutation in TP53. Mutations in TP53, PTEN, CDH1, and STK11 are associated with hereditary cancer syndromes in which there is an increased risk for breast cancer; however, the risk for developing an invasive breast cancer associated with these syndromes varies. Some individuals with a pathogenic variant in one of these genes develop multiple primary cancers or bilateral cancers. Therefore, testing for mutations in these 4 genes may also be useful when there is a suspicion of a hereditary susceptibility to breast cancer. Lynch Syndrome Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC) is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3’ end of the EPCAM gene, which lead to inactivation of the MSH2 promotor, have also been associated with Lynch syndrome. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer-associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome-related genes. The lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are less than 15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. The National Comprehensive Cancer Network and the American Cancer Society provide recommendations regarding the medical management of individuals with HBOC and Lynch syndrome.

**Useful For:** Establishing a hereditary susceptibility to cancer Evaluation of families with a history suggestive of a predisposition to both breast and colorectal cancer Identification of familial BRCA1, BRCA2, TP53, PTEN, CDH1, STK11, MLH1, MSH2, MSH6, PMS2, or EPCAM mutation to allow for predictive testing in family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.

**BRST4 64331**

**Hereditary Breast Cancer 4 Gene Panel**

**Clinical Information:** Hereditary breast cancer susceptibility is associated with germline mutations in several genes including BRCA1, BRCA2, and others. Pathogenic BRCA1 and BRCA2 variants account for the majority of hereditary breast cancer; however, mutations in other genes may be present in families in which a BRCA1 or BRCA2 gene mutation is not identified. For instance, it has been demonstrated that 8% of women with very early-onset (less than 30 years of age) breast cancer who test negative for a mutation in BRCA1 and BRCA2 have a mutation in TP53. Mutations in TP53, PTEN, CDH1, and STK11 are associated with hereditary cancer syndromes in which there is an increased risk for breast cancer; however, the risk for developing an invasive breast cancer associated with these syndromes varies. Some individuals with a pathogenic variant in one of these genes develop multiple primary cancers or bilateral cancers. Therefore, testing for mutations in these 4 genes may be useful when there is a suspicion of a hereditary susceptibility to breast cancer in which a mutation in BRCA1 and BRCA2 is not identified.

**Useful For:** Establishing a hereditary susceptibility to cancer Evaluation of families with a history suggestive of a hereditary breast cancer syndrome in which a BRCA1 or BRCA2 gene mutation is not identified Identification of familial TP53, PTEN, CDH1, or STK11 mutation to allow for predictive testing in family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.

**BRST6 64332**

**Hereditary Breast Cancer 6 Gene Panel**

**Clinical Information:** Hereditary breast and ovarian cancer (HBOC) is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the BRCA1 or BRCA2 genes. Mutations within these 2 genes account for the majority of hereditary breast and ovarian cancer families. HBOC is predominantly characterized by young-onset breast cancer and ovarian cancer. However, HBOC is also associated with increased risks for prostate cancer, pancreatic cancer, fallopian tube cancer, and male breast cancer. HBOC is highly penetrant; the risk for developing an invasive breast cancer is about 60% to 65% and the risk for developing ovarian cancer is about 40% by age 70. Some individuals develop multiple primary or bilateral cancers. The National Comprehensive Cancer Network and the American Cancer Society provide recommendations regarding the medical management of individuals with HBOC. Hereditary breast cancer susceptibility is associated with germline mutations in several other genes including TP53, PTEN, CDH1, and STK11. While pathogenic BRCA1 and BRCA2 variants account for the majority of hereditary breast cancer, mutations in other genes may be present in families in which a BRCA1 or BRCA2 gene mutation is not identified. For instance, it has been demonstrated that 8% of women with very early-onset (less than 30 years of age) breast cancer who test negative for a mutation in BRCA1 and BRCA2 have a mutation in TP53. Mutations in TP53, PTEN, CDH1, and STK11 are associated with hereditary cancer syndromes in which there is an increased risk for breast cancer; however, the risk for developing an invasive breast cancer associated with these syndromes varies. Some individuals with a pathogenic variant in one of these genes develop multiple primary cancers or bilateral cancers. Therefore, testing for mutations in these 4 genes may also be useful when there is a suspicion of a hereditary susceptibility to breast cancer.

**Useful For:** Establishing a hereditary susceptibility to cancer Identification of familial BRCA1, BRCA2, TP53, PTEN, CDH1, or STK11 mutation to allow for predictive testing in family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**

An interpretive report will be provided.

COLAB 35382

**Hereditary Colon Cancer CGH Array**

**Reference Values:**
Only orderable as a reflex. For further information see:
- AXINZ / AXIN2 Gene, Full Gene Analysis
- BMPRZ / BMPR1A Gene, Full Gene Analysis
- CHEKZ / CHEK2 Gene, Full Gene Analysis
- MLH3Z / MLH3 Gene, Full Gene Analysis
- PTENZ / PTEN Gene, Full Gene Analysis
- SMADZ / SMAD4 Gene, Full Gene Analysis
- STKZ / STK11 Gene, Full Gene Analysis
- TP53Z / TP53 Gene, Full Gene Analysis
- CDH1Z / CDH1 Gene Analysis
- M1M2Z / MLH1/MSH2 Genes, Full Gene Analysis
  - MLH1Z / MLH1 Gene, Full Gene Analysis
  - MSH2Z / MSH2 Gene, Full Gene Analysis
  - MSH6Z / MSH6 Gene, Full Gene Analysis
- APCZ / APC Gene, Full Gene Analysis

For information regarding hereditary colon cancer, see FMTT / Familial Mutation, Targeted Testing.

HCRC 35450

**Hereditary Colon Cancer Multi-Gene Panel**

**Clinical Information:** Colorectal cancer occurs in approximately 5% to 6% of individuals in the general population. In rare cases, individuals with a family history of colorectal cancer may be at increased risk for colon and other cancers due to a single-gene predisposition syndrome, known as hereditary colorectal cancer. The 2 most common hereditary colorectal cancer syndromes are Lynch syndrome and familial adenomatous polyposis (FAP). However, there are multiple other genes that are also known to cause to hereditary colorectal cancer or contribute to an increased risk for colorectal cancer. This panel uses next-generation sequencing (NGS), array comparative genomic hybridization (aCGH), and other technologies to evaluate for germline mutations in 17 genes known to be associated with an increased risk for colon cancer development. Two of the genes listed, CHEK2 and MLH3, are not associated with a known hereditary cancer syndrome defined by a distinct spectrum of tumors. However, literature suggests that mutations in these genes may confer an increased risk for colon cancer and, therefore, are predicted to contribute to cancer risk in patients and families. Gene Known Association MLH1 Lynch syndrome MSH2 Lynch syndrome MSH6 Lynch syndrome PMS2 Lynch syndrome EPCAM Lynch syndrome APC Familial adenomatous polyposis MYH/MutYH MYH-associated polyposis SCG5/GREM1 Hereditary mixed polyposis syndrome STK11 Peutz-Jeghers syndrome SMAD4 Juvenile polyposis syndrome BMPR1A Juvenile polyposis syndrome PTEN PTEN hamartoma tumor syndrome (ie, Cowden syndrome) CDH1 Hereditary diffuse gastric cancer AXIN2 Oligodontia-colorectal cancer syndrome TP53 Li-Fraumeni syndrome CHEK2 Low-risk gene MLH3 Low-risk gene Indications for testing include but are not limited to: - Patients in whom no specific colorectal cancer syndrome is evident but for whom there is a clear familial component - Patients whose family history is consistent with familial colorectal cancer type X(1) - Patients with a strong suspicion for a single-gene hereditary colon cancer syndrome based on an autosomal dominant pattern of colon cancer in the family - Patients with a personal or family history of colonic polyposis
Useful For: Providing a comprehensive evaluation for hereditary colon cancer in patients with a personal or family history suggestive of a hereditary colon cancer syndrome. Serving as a second-tier test for patients in whom previous targeted gene mutation analyses for specific hereditary colorectal cancer-related genes were negative. Establishing a diagnosis of a hereditary colon cancer syndrome in some cases, allowing for targeted cancer surveillance of associated extra-colonic organs known to be at increased risk for cancer. Identifying mutations within genes known to be associated with increased risk for colon cancer allowing for predictive testing of at-risk family members.

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

Hereditary Erythrocytosis Mutations

Clinical Information: Erythrocytosis (ie, increased RBC mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, polycythemia vera: PV), or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other EPO-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be suspected. Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases is associated with pheochromocytoma and/or paraganglioma formation. It is caused by mutations in several genes and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these cases, although it is possible for new mutations to arise in an individual. The genes coding for hemoglobin, beta globin and alpha globin (high-oxygen-affinity hemoglobin variants), hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase: BPGM), and the erythropoietin receptor, EPOR, and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF/EPAS1, prolyl hydroxylase domain: PHD2/EGLN1, and von Hippel Lindau: VHL) can result in hereditary erythrocytosis (see Table). High-oxygen-affinity hemoglobin variants and BPGM abnormalities result in a decreased p50 result, whereas those affecting EPOR, HIF, PHD, and VHL have normal p50 results. The true prevalence of hereditary erythrocytosis-causing mutations is unknown. Genes Associated with Hereditary Erythrocytosis Gene Inheritance Serum EPO p50 JAK2 V617F Acquired Decreased Normal JAK2 exon 12 Acquired Decreased Normal EPOR Dominant Decreased to normal level Normal PHD2/EGLN1 Dominant Normal level Normal BPGM Recessive Normal level
Decreased Beta Globin Dominant Normal level to increased Decreased Alpha Globin Dominant Normal level to increased Decreased HIF2A/EPAS1 Dominant Normal level to increased Normal VHL Recessive Markedly Increased Normal The oxygen-sensing pathway functions through an enzyme, hypoxia-inducible factor (HIF), which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including EPO, VEGF, and GLUT1. HIF-alpha is regulated by von Hippel-Lindau (VHL) protein-mediated ubiquitination and proteosomal degradation, which requires prolyl hydroxylation of HIF proline residues. The HIF-alpha subunit is encoded by the HIF2A (official name EPAS1) gene. Enzymes important in the hydroxylation of HIF-alpha are the prolyl hydroxylase domain proteins, of which the most significant isof orm is PHD2, which is encoded by the PHD2 (official name EGLN1) gene. Mutations resulting in altered HIF-alpha, PHD2, and VHL proteins can lead to clinical erythrocytosis. A small subset of mutations, in PHD2 and HIF2A, has also been detected in erythrocytic patients presenting with paragangliomas or pheochromocytomas. Truncating mutations in the EPOR gene coding for the erythropoietin receptor can result in erythrocytosis through loss of the negative regulatory cytoplasmic SHP-1 binding domain leading to EPO hypersensitivity. All currently known mutations have been localized to exon 8, are mainly missense or small deletion and insertions resulting in stop codons, and are heterozygous. EPOR mutations are associated with decreased to normal EPO levels and normal p50 values (see Table).

Useful For: The definitive evaluation of an individual with JAK2-negative erythrocytosis associated with lifelong sustained increased RBC mass, elevated RBC count, hemoglobin, or hematocrit

Interpretation: An interpretive report will be provided and will include specimen information, assay information, and whether the specimen was positive for any mutations in the gene. If positive, the mutation will be correlated with clinical significance, if known.

Reference Values:
An interpretive report will be provided.


NGHHA
Hereditary Hemolytic Anemia Comprehensive Sequencing, Varies

Clinical Information: Next-generation sequencing (NGS) is a methodology that can interrogate large regions of genomic DNA in a single assay. The presence and pattern of gene mutations can provide critical diagnostic, prognostic, and therapeutic information for managing physicians. This test is best interpreted in the context of protein studies and peripheral blood findings. This can be provided by ordering the HAEVP / Hemolytic Anemia Evaluation Profile test. Please fill out the information sheet and indicate that NGS testing was also ordered. Providing CBC data and clinical notes will also allow more precise interpretation of results. Hereditary hemolytic anemias are caused by defects in one or
more of the genes that control RBC production, metabolism, or structure, resulting in faulty erythropoiesis, cell membranes, or enzymes required for normal RBC function. This panel aids in the diagnosis and treatment for hereditary (congenital) hemolytic anemia.(1,2) The panel includes genes known to cause hereditary anemia including those implicated in RBC enzyme,(3) RBC membrane/RBC hydration,(4) and congenital dyserythropoietic anemia(5) disorders. This panel can aid in the differential diagnosis of early onset and lifelong myopathic or neurologic syndromes, especially if associated with hemolysis. Specifically, this panel assays genes associated with hereditary spherocytosis (HS), hereditary elliptocytosis (HE), hereditary pyropoikilocytosis (HPP), Southeast Asian ovalocytosis, hereditary stomatocytosis (both overhydrated and dehydrated/hereditary xerocytosis subtypes), and cryohydrocytosis. Hereditary stomatocytosis is a RBC membrane permeability disorder that can manifest as the more common dehydrated hereditary stomatocytosis (DHS), also known as hereditary xerocytosis (HX) and the rarer overhydrated hereditary stomatocytosis (OHSt) subtypes. These disorders are important to confirm or exclude as splenectomy has been associated with an increased risk for serious venous thrombosis and thromboembolism events and is contraindicated in published guidelines.(7) It also includes genes associated with RBC enzymopathies, ranging from the common glucose 6 phosphate dehydrogenase (G6PD) and pyruvate kinase (PK) deficiencies, to the rarer disorders of adenylate kinase (AK1), hexokinase (HK1), phosphofructokinase (PFKM), phosphoglycerate kinase (PGK1), pyruvate kinase (PKLR), glutathione pathway, and triosephosphate isomerase (TP1). This panel also includes multiple genes associated with congenital dyserythropoietic anemia (CDA), types 1a, 1b, 2, 3, and 4. CDA is a disorder of ineffective erythropoiesis associated with distinctive bone marrow morphologic changes. A limited number of the most common genes associated with Fanconi anemia (FA) and Diamond-Blackfan anemia (DBA) are also analyzed by this panel; however, this panel is not intended as a thorough investigation of FA or DBA.

**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hereditary hemolytic anemias, including RBC membrane/hydration disorders, RBC enzymopathies and congenital dyserythropoietic anemia Comprehensive testing for patients in whom previous targeted gene mutation analyses were negative for a specific hereditary hemolytic anemia Establishing a diagnosis of a hereditary hemolytic anemia or related disorder, allowing for appropriate management and surveillance of disease features based on the gene involved, especially if splenectomy is a consideration (2) Identifying mutations within genes associated with phenotypic severity, allowing for predictive testing and further genetic counseling

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(6,7) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

Hereditary Hemorrhagic Telangiectasia Gene Panel

Clinical Information: Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is an autosomal dominant vascular dysplasia characterized by the presence of arteriovenous malformations (AVM) of the skin, mucosa, and viscera. Small AVM, or telangiectasias, develop predominantly on the face, oral cavity, and hands, and spontaneous, recurrent epistaxis (nose bleeding) is a common presenting sign. Symptomatic telangiectasias occur in the gastrointestinal tract of about 30% of HHT patients. Additional serious complications associated with HHT include transient ischemic attacks, embolic stroke, heart failure, cerebral abscess, massive hemoptysis, massive hemothorax, seizure, and cerebral hemorrhage. These complications are a result of larger AVM, which are most commonly pulmonary, hepatic, or cerebral in origin, and occur in approximately 30%, 40%, and 10% of individuals with HHT, respectively. HHT is inherited in an autosomal dominant manner and occurs with wide ethnic and geographic distribution. The overall incidence of HHT in North America is estimated to be between 1 in 5,000 and 1 in 10,000. Penetrance seems to be age related, with increased manifestations occurring over one's lifetime. For example, approximately 50% of diagnosed individuals report having nosebleeds by age 10 years, increasing to 80% to 90% by age 21 years, and as many as 90% to 95% of affected individuals eventually developing recurrent epistaxis. HHT is phenotypically heterogeneous both between families and amongst affected members of the same family. Furthermore, complications associated with HHT have variable ranges of age of onset. Thus, HHT can be diagnostically challenging. Genetic testing allows for the confirmation of a suspected genetic disease. Confirmation of a diagnosis allows for proper treatment and management of the disease, preconception or prenatal counseling, and family counseling. In addition, it has been estimated that genetic screening of suspected HHT individuals and their families is more economically effective than conventional clinical screening. Two genes are most commonly associated with HHT: the endoglin gene (ENG), and the activin A receptor, type II-like 1 gene (ACVRL1 or ALK1). ENG and ACVRL1 encode membrane glycoproteins involved in transforming growth factor-beta signaling related to vascular integrity. Variants in ENG are associated with HHT type 1 (HHT1), which has been reported to have a higher incidence of pulmonary AVM, whereas ACVRL1 variants occur in HHT type 2 (HHT2), which has been reported to have a higher incidence of hepatic AVM. The majority of variants in ENG and ACVRL1 are missense, nonsense, splice site, or small intragenic deletions and insertions. Approximately 10% of ENG and ACVRL1 variants are large genomic deletions and duplications (also known as dosage alterations). Approximately 60% to 80% of patients with HHT will have a variant detected in ENG or ACVRL1. Pathogenic variants in the SMAD4 gene are the third most common identifiable cause of HHT, accounting for approximately 10% of HHT patients who test negative for ENG and ACVRL1, and approximately 1% to 2% of total HHT cases. Pathogenic SMAD4 variants cause autosomal dominant juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome (JPHT), which includes features of juvenile polyposis syndrome (JPS) and HHT. JPS is characterized by hamartomatous polyps of the gastrointestinal tract and increased risk of gastrointestinal cancer. SMAD4 variants have also been detected in families presenting with JPS or HHT only. Pathogenic variants in the GDF2 gene (also known as BMP9) are a rare cause of HHT. In a study of 191 individuals with clinically suspected HHT and no variants in ENG, ACVRL1, or SMAD4, 3 unrelated individuals were found to carry a rare missense variant in GDF2. Pathogenic variants in the RASA1 gene cause capillary malformation-arteriovenous malformation syndrome (CMAVM). CMAVM is characterized by the presence of multiple small (1-2 cm in diameter) capillary malformations mostly localized to the face and limbs. Patients may also have arteriovenous malformations (AVM) and arteriovenous fistulas (AVF). In some cases, pathogenic RASA1 variants may be found in individuals clinically suspected to have HHT. Individuals with a pathogenic RASA1 variant may have a clinical diagnosis of Parkes Weber syndrome (PWS), with multiple micro-AVF associated with a cutaneous capillary stain and excessive soft tissue and skeletal growth of an affected limb. Table1. Genes included in the HHT Gene Panel Gene Symbol (alias) Protein OMIM Inheritance Phenotype/Disorder ACVRL1 Activin A receptor like type 1 601284 AD Telangiectasia, hereditary hemorrhagic, type 2 ENG Endoglin 131195 AD Telangiectasia, hereditary hemorrhagic, type 1 GDF2 Growth differentiation factor 2 605120 AD Telangiectasia, hereditary hemorrhagic, type 5 RASA1 RAS p21 protein activator 1 139150 AD Capillary malformation-arteriovenous malformation, Parkes Weber syndrome SMAD4 SMAD family member 4 600993 AD Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome, Myhre syndrome AD: autosomal dominant AR: autosomal recessive
**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hereditary hemorrhagic telangiectasia (HHT) or a related disorder. Second-tier testing for patients in whom previous targeted gene variant analyses for specific HHT genes were negative. Establishing a diagnosis of HHT and in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved. Identifying variants within genes known to be associated with HHT and allowing for predictive testing of at-risk family members.

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**HMSNP 64359**

**Hereditary Motor and Sensory Neuropathy Panel by Next-Generation Sequencing (NGS)**

**Clinical Information:** Inherited peripheral neuropathies are a diverse group of disorders with heterogeneous genetic causes that can be divided into major categories based on the pattern of inheritance and nerve conduction studies. Hereditary motor and sensory neuropathy (HMSN), also known as Charcot-Marie-Tooth (CMT) disease, is a major category of inherited peripheral neuropathies and is the most commonly inherited neuromuscular disorder. It is characterized by motor and sensory peripheral nerve involvement. The clinical phenotype is variable, and includes wasting and weakness of the distal limb muscles, skeletal deformities, and hearing loss. HMSN/CMT is classified into 5 groups: 1) HMSN 1, which is a dominantly inherited demyelinating form; 2) HMSN 2, a dominantly inherited axonal predominant neuropathy; 3) HMSN 3 (also called Dejerine-Sottas disease), which is often inherited dominantly, with onset in infancy or childhood and is characterized by extremely slow nerve conduction velocities resulting in loss of ambulatory milestones and more generalized neurologic deficit; 4) HMSN 4, an autosomal recessive inherited demyelinating form that may also present with extraneural features, including facial dysmorphism and scoliosis, particularly those with HMSN 4C, the most frequent form of HMSN 4; 5) HMSN 5, a form associated with spasticity, also known as “complex hereditary spastic paraplegia (HSP).” Given the considerable phenotypic and genetic heterogeneity of HMSN/CMT disease, a comprehensive diagnostic genetic test is useful to establish the genetic cause in this group of inherited disorders.
peripheral neuropathies. See Targeted Genes Interrogated by Motor and Sensory Neuropathy Panel in Special Instructions for details regarding the targeted genes identified by this test.

**Useful For:** Diagnosis of hereditary motor and sensory neuropathy (HMSN) or Charcot-Marie-Tooth (CMT) disease associated with known causal genes Second-tier testing for patients in whom previous targeted gene mutation analyses for specific inherited hereditary motor and sensory neuropathy-related genes were negative Identifying mutations within genes known to be associated with inherited hereditary motor and sensory neuropathy, allowing for predictive testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Hereditary Motor Neuropathy Panel by Next-Generation Sequencing (NGS)**

**Clinical Information:** Inherited peripheral neuropathies are a relatively common, diverse group of disorders with heterogeneous genetic causes. Based on the pattern of inheritance and nerve conduction studies, inherited peripheral neuropathies with isolated nerve involvement can be divided into major categories. Distal hereditary motor neuropathies (dHMN) are one of the major categories of peripheral inherited neuropathies and are characterized by length-dependent, slowly progressive motor neuropathies with variable nerve conduction velocities. The clinical phenotype is variable, but includes progressive weakness and atrophy of the distal muscles, foot deformities, and decreased reflexes. There is significant phenotypic overlap with hereditary motor sensory neuropathy (HMSN), also known as Charcot-Marie-Tooth (CMT); however, sensory loss is usually absent in dHMN. dHMN are subdivided into 11 subtypes based on inheritance pattern and clinical features and include types 1-7, dHMN plus pyramidal signs, X-linked, congenital distal SMA, and Jerash type. Given the considerable phenotypic and genetic heterogeneity of dHMN, a comprehensive diagnostic genetic test is helpful to establish the genetic cause in this group of inherited neuropathies. See Targeted Genes Interrogated by Hereditary Motor Neuropathy Panel in Special Instructions for details regarding the targeted genes identified by this test.

**Useful For:** Diagnosing distal hereditary motor neuropathy (dHMN) associated with known causal genes Second-tier testing for patients in whom previous targeted gene mutation analyses for specific inherited hereditary motor neuropathy-related genes were negative Identifying mutations within genes known to be associated with inherited hereditary motor neuropathy, allowing for predictive testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Hereditary Pancreatitis Panel

Clinical Information: Mutations in several genes, including PRSS1, CFTR, CTRC, and SPINK1 have demonstrated genetic susceptibility to chronic pancreatitis. Disease susceptibility may be monogenic, as is the case with PRSS1, digenic or multigenic, and multifactorial in which multiple genes and environmental factors play a role in disease expression. PRSS1: Hereditary pancreatitis (HP) is defined as 2 or more individuals in a family affected with pancreatitis involving at least 2 generations. The most common monogenic cause of HP is the presence of a mutation in the cationic trypsinogen (PRSS1) gene. Mutations in the PRSS1 gene are inherited in an autosomal dominant manner. It has been reported that as many as 80% of patients with symptomatic hereditary pancreatitis have a causative PRSS1 mutation. HP cannot be clinically distinguished from other forms of pancreatitis. However, PRSS1 mutations are generally restricted to individuals with a family history of pancreatitis and are infrequently found in patients with alcohol-induced or tropical pancreatitis. Although several mutations have been identified, the R122H, N29I, and A16V mutations are the most common disease-causing mutations in PRSS1 associated with HP. Data suggests that the R122H mutation results in more severe disease and earlier onset of symptoms than the A16V mutation. Patients with HP are also at an increased risk for developing pancreatic cancer. Studies have estimated the lifetime risk of developing pancreatic cancer to be as high as 40%. SPINK1: Biallelic mutations in the SPINK1 gene have been associated with increased susceptibility to chronic pancreatitis especially in families without PRSS1 mutations; however, it is unknown if biallelic mutations alone are sufficient to cause chronic pancreatitis. Additionally, heterozygous SPINK1 mutations appear to modify disease severity when observed in combination with mutations in other genes. Unlike PRSS1 mutations, SPINK1 mutations have been associated with alcohol-induced and tropical pancreatitis. CFTR: Pancreatitis is a known manifestation of an atypical CFTR-related disorder in which 2 mutations in the CFTR gene are identified. However, CFTR mutations can also co-occur with mutations in CTRC, SPINK1, or CASR to confer pancreatitis disease susceptibility. When observed in the context of a SPINK1 mutation, for example, heterozygous mutations in CFTR are associated with a 2- to 5-fold increased risk for pancreatitis as compared to the general population. CTRC: Mutations in CTRC have been observed in individuals with chronic pancreatitis in association with other risk factors such as mutations in CFTR or SPINK1 or specific environmental risk factors. Thus, chronic pancreatitis may be attributable to the presence of CTRC mutations in the context of other risk factors as opposed to CTRC mutations alone.

Useful For: Confirmation of suspected clinical diagnosis of familial or hereditary pancreatitis in patients with chronic pancreatitis Identification of gene mutations contributing to pancreatitis in an individual or family Identification of gene mutations to allow for predictive and diagnostic testing in family members

Interpretation: All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics (AMCG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.

Hereditary Pheochromocytoma/Paraganglioma Multi Gene Panel

Clinical Information: Paragangliomas and pheochromocytomas (PGL/PCC) are rare, but potentially lethal, neuroendocrine tumors that arise from autonomous ganglia. Tumors located within the adrenal medulla (the largest sympathetic ganglion) are called pheochromocytomas (PCC), while those that stem from either parasympathetic or sympathetic ganglia are designated paragangliomas (PGL). PCC and sympathetic PGL secrete catecholamines (epinephrine, norepinephrine, or dopamine) and their metabolites. The excess catecholamines result in hypertension, which might be sustained or episodic; however, most patients with sustained hypertension will also occasionally experience episodic "spells" caused by sudden, massive catecholamine release and characterized by worsened hypertension, palpitations/cardiac arrhythmias, severe headaches, pallor, and sweating. A minority of patients can be largely asymptomatic and might be diagnosed by the incidental discovery of an adrenal mass, or enlarged subdiaphragmatic sympathetic ganglia. Untreated PGL/PCC has substantial morbidity and mortality, which can be prevented by tumor removal. PGL/PCC have a germline genetic basis in at least 30% of cases. Pathogenic germline genetic alterations in the following genes are known to predispose to PGL/PCC: RET, VHL, NF1, SDHB, SDHC, SDHD, SDHAF2 (aka SHD5), TMEM127, and MAX. With the exception of the RET kinase, which acquires its tumorigenicity through activating variants, all these genes follow the classical 2-hit model with pathogenic loss of function variants, followed by somatic inactivation of the remaining copy in target organs. RET, VHL, NF1, TMEM127, and MAX predominately cause PCC, while the various SDH genes most often lead to PGL. Inheritance of these genetic tumor syndromes is autosomal dominant, with the exceptions of SDHD, SDHAF2 (SDH5), and, possibly, MAX, which can show parent-of-origin effects, causing disease almost exclusively when they are paternal in origin. PGL/PCC-specific disease penetrance ranges from approximately 25 to 40% (SDHB) to 80 to 100% (MAX), with exact numbers unknown for some of the genes involved. While PGL/PCC in general are nonmalignant tumors, malignant PGL/PCC are observed in a significant proportion of patients in most of the predisposing familial tumor syndromes, with the frequency of malignant transformation approaching 50% in SDHB-related tumors. Several of these tumor genes, most notably RET, VHL, NF1, SDHB, and TMEM127, also predispose to a variety of other tumors. Genetic testing can either proceed gene-by-gene, potentially guided by the clinical pattern of lesions, and biochemical parameters, as most recently outlined in the latest Endocrine Society Clinical Practice Guideline for pheochromocytoma and paraganglioma (2014) or, it can be accomplished by screening several genes with a multigene panel.

Useful For: Providing a comprehensive evaluation for paraganglioma/pheochromocytoma in patients with a personal or family history suggestive of a hereditary paraganglioma/pheochromocytoma syndrome Serving as a second-tier test for patients in whom previous targeted gene variant analyses for specific hereditary paraganglioma/pheochromocytoma-related genes were negative Establishing a diagnosis of a hereditary paraganglioma/pheochromocytoma syndrome in some cases, allowing for targeted cancer surveillance of associated tissues and organs known to be at increased risk for tumor or cancer Identifying variants within genes known to be associated with increased risk for paraganglioma/pheochromocytoma allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. 1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.

HSNP 64360

**Hereditary Sensory/Autonomic Neuropathy Panel by Next-Generation Sequencing (NGS)**

**Clinical Information:** Inherited peripheral neuropathies are a relatively common diverse group of disorders with heterogeneous genetic causes. Based on the pattern of inheritance and nerve conduction studies, inherited peripheral neuropathies with isolated nerve involvement can be divided into major categories. Hereditary sensory and autonomic neuropathies (HSAN), or hereditary sensory neuropathies (HSN) if autonomic dysfunction is absent, is one of these major categories of inherited peripheral neuropathies. They affect sensory and autonomic nerves and the hallmark feature is the presence of prominent small-fiber involvement. HSAN are subdivided into 5 groups based on age of onset, inheritance pattern, and clinical features: HSAN 1 varieties (HSAN 1A-E) follow an autosomal dominant inheritance pattern with juvenile or adult onset, and severe sensory loss and autonomic dysfunction; HSAN 2-5 have an autosomal recessive inheritance pattern and are usually congenital; HSAN3, also known as familial dysautonomia or Rilay-Day syndrome, is characterized by prominent autonomic and small-fiber sensory involvement; HSAN 4 and 5 are characterized by insensitivity to pain and widespread autonomic disturbance, with HSAN 4 also featuring mental retardation. Given the considerable phenotypic and genetic heterogeneity of HSAN/HSN, a comprehensive diagnostic genetic test is useful to establish the genetic cause in this group of inherited neuropathies. See Targeted Genes Interrogated by Hereditary Sensory Neuropathy Panel in Special Instructions for details regarding the targeted genes identified by this test.

**Useful For:** Diagnosis of inherited hereditary sensory (HSN) and autonomic neuropathy (HSAN) associated with known causal genes Second-tier testing for patients in whom previous targeted gene mutation analyses for specific inherited hereditary motor and sensory neuropathy-related genes were negative Identifying mutations within genes known to be associated with inherited hereditary motor and sensory neuropathy, allowing for predictive testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.


HSPP 64362

**Hereditary Spastic Paraplegia Neuropathy Panel by Next-Generation Sequencing (NGS)**

**Clinical Information:** Inherited peripheral neuropathies are a relatively common diverse group of disorders with heterogeneous genetic causes. Hereditary spastic paraplegia (HSP) is characterized by
progressive lower extremity weakness and spasticity, and may present with prominent peripheral neuropathy as one of the complicated forms, also known as hereditary motor sensory neuropathy 5 (HMSN 5). The complicated forms are associated with a variety of other neurological systemic abnormalities and usually follow an autosomal recessive inheritance pattern. The uncomplicated or pure form presents with lower limb weakness and spasticity, and is predominantly characterized by an autosomal dominant inheritance pattern. Given the considerable phenotypic and genetic heterogeneity of HSP, a comprehensive diagnostic genetic test is useful to establish the genetic cause in this HSP with neuropathy. See Targeted Genes Interrogated by Spastic Paraplegia Neuropathy Panel in Special Instructions for details regarding the targeted genes identified by this test.

**Useful For:** Diagnosis of hereditary spastic paraplegia with neuropathy associated with known causal genes Second-tier testing for patients in whom previous targeted gene mutation analyses for specific inherited hereditary spastic paraplegia-related genes were negative Identifying mutations within genes known to be associated with hereditary spastic paraplegia, allowing for predictive testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.


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**Herpes Simplex Virus (HSV) and Varicella-Zoster Virus (VZV), Molecular Detection, PCR**

**Clinical Information:** Herpes simplex virus (HSV) types 1 and 2 are members of the Herpesviridae family, and produce infections that may range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV types 1 and 2 can differ significantly in their clinical manifestations and severity. HSV type 2 primarily causes urogenital infections and is found almost exclusively in adults. HSV type 1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. The diagnosis of HSV infections is routinely made based on clinical findings and supported by laboratory testing using PCR or viral culture. HSV causes various clinical syndromes. Anatomic sites infected include skin, lips and oral cavity, eyes, genital tract, and central nervous system.(1) Varicella-zoster virus (VZV) causes both varicella (chickenpox) and herpes zoster (shingles). VZV produces a generalized vesicular rash on the dermis (chickenpox) in normal children, usually before age 10. After primary infection with VZV, the virus persists in latent form and may emerge (usually in adults age 50 and older) clinically to cause a unilateral vesicular eruption, generally in a dermatomal distribution (shingles).

**Useful For:** Rapid diagnosis of herpes simplex virus and varicella-zoster virus infections

**Interpretation:** Herpes Simplex Virus (HSV) PCR: This is a qualitative assay; results are reported either as negative, positive, or indeterminate for HSV type 1 or HSV type 2. Detection of HSV DNA in clinical specimens supports the clinical diagnosis of infection due to the virus. Varicella-Zoster Virus (VZV) PCR: Detection of VZV DNA in clinical specimens supports the clinical diagnosis of infection due to this virus. VZV DNA is not detected in cerebrospinal fluid from patients without central nervous
system disease caused by this virus. This LightCycler PCR assay does not yield positive results with other herpesvirus gene targets (cytomegalovirus, Epstein-Barr virus).

**Reference Values:**
HERPES SIMPLEX VIRUS (HSV) PCR
Negative

VARICELLA-ZOSTER VIRUS PCR
Negative

**Clinical References:**

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**Herpes Simplex Virus (HSV) Antibody Screen, IgM, by EIA, Serum**

**Clinical Information:** The herpesvirus family contains herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and human herpesviruses 6 through 8. HSV types 1 and 2 produce infections that are expressed in various clinical manifestations ranging from mild stomatitis to disseminated and fatal disease. The more common clinical conditions include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV types 1 and 2 can differ significantly in their clinical manifestations and severity. HSV type 1 is closely associated with infections of the mouth and lips, although genital infections can be common in some populations. HSV type 2 is the cause of the majority of urogenital infections and is almost exclusively found in adults.

**Useful For:** Aiding in the diagnosis of infection with herpes simplex virus

**Interpretation:** A positive result (ie, the presence of IgM class herpes simplex virus [HSV] 1 and/or 2 antibodies) indicates recent infection. The presence of HSV 1 and/or 2 antibodies may indicate a primary or reactivated infection, but cannot distinguish between them. Specimens with positive results are automatically tested for IgM antibodies by a second method (immunofluorescence assay [IFA]). The continued presence or level of antibody cannot be used to determine the success or failure of therapy. The prevalence of HSV IgM antibodies can vary depending on a number of factors such as age, gender, geographical location, socio-economic status, race, sexual behavior, testing method used, specimen collection and handling procedures, and the clinical and epidemiological history of individual patients. A negative result does not necessarily rule out a primary or reactivated infection since specimens may have been collected too early in the course of disease, when antibodies have not yet reached detectable levels, or too late, after IgM levels have declined below detectable levels.

**Reference Values:**

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Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Herpes Simplex Virus (HSV) Type 1- and Type 2-Specific Antibodies, IgG, Serum

**Clinical Information:** Herpes simplex virus (HSV) types 1 and 2 are members of the Herpesviridae family, and produce infections that may range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV types 1 and 2 can differ significantly in their clinical manifestations and severity. HSV type 2 primarily causes urogenital infections and is found almost exclusively in adults. HSV type 1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. The diagnosis of HSV infections is routinely made based on clinical findings and supported by laboratory testing using PCR or viral culture. However, in instances of subclinical or unrecognized HSV infection, serologic testing for IgG-class antibodies to type-specific HSV glycoprotein G (gG) may be useful. There are several circumstances in which it may be important to distinguish between infection caused by HSV types 1 and 2. (1) For example, the likelihood of reactivation of the infection (type 2 greater than type 1) and the method of antiviral therapy may differ depending on the specific type of HSV causing disease. In addition, the results of HSV type-specific IgG testing is sometimes used during pregnancy to identify risks of congenital HSV disease and allow for focused counseling prior to delivery. (2-3)

**Useful For:** Determining whether a patient has been previously exposed to herpes simplex virus (HSV) types 1 and 2. Distinguishing between infection caused by HSV types 1 and 2, especially in patients with subclinical or unrecognized HSV infection.

**Interpretation:** This assay detects IgG-class antibodies to type-specific herpes simplex virus (HSV) glycoprotein G (gG), and may allow for the differentiation of infection caused by HSV types 1 and 2. The presence of IgG-class antibodies to HSV types 1 or 2 indicates previous exposure, and does not necessarily indicate that HSV is the causative agent of an acute illness.

**Reference Values:** Negative (reported as positive, negative, or equivocal)

Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV types 1 and 2 can differ significantly in their clinical manifestations and severity. HSV type 2 primarily causes urogenital infections and is found almost exclusively in adults. HSV type 1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. The diagnosis of HSV infections is routinely made based on clinical findings and supported by laboratory testing using PCR or viral culture. However, in instances of subclinical or unrecognized HSV infection, serologic testing for IgG-class antibodies to type-specific HSV glycoprotein G (gG) may be useful. There are several circumstances in which it may be important to distinguish between infection caused by HSV types 1 and 2. For example, the likelihood of reactivation of the infection (type 2 > type 1) and the method of antiviral therapy may be different depending on the specific type of HSV causing disease. In addition, the results of HSV type-specific IgG testing is sometimes used during pregnancy to identify risks of congenital HSV disease and allow for focused counseling prior to delivery.(1,2,3) Useful For: Supplementing culture or molecular detection of herpes simplex virus (HSV) for the diagnosis of acute infection Determining whether a patient has been previously exposed to HSV types 1 or 2 Distinguishing between infection caused by HSV types 1 and 2, especially in patients with subclinical or unrecognized HSV infection

Interpretation: The presence of IgM herpes simplex virus (HSV) antibodies indicates acute infection with either HSV type 1 or 2. The IgG antibody assay detects IgG-class antibodies to type-specific HSV glycoprotein G (gG), and may allow for the differentiation of infection caused by HSV types 1 and 2. The presence of IgG-class antibodies to HSV types 1 or 2 indicates previous exposure, and does not necessarily indicate that HSV is the causative agent of an acute illness.

Reference Values:
HSV TYPE 1 ANTIBODY, IgG Negative

HSV TYPE 2 ANTIBODY, IgG Negative
Reference values apply to all ages.

HSV ANTIBODY SCREEN, IgM, by EIA Negative
Reference values apply to all ages.


Herpes Simplex Virus (HSV), Culture From Neonates

Clinical Information: Herpes simplex virus (HSV) types 1 (HSV-1) and 2 (HSV-2) are DNA viruses that cause localized infections of the skin, oral mucosa, oral cavity, eyes, genital tract, and central nervous system (CNS).(1,2) Systemic disease may occur. Primary infection typically results in no symptoms or localized pain and lesions at the site of infection (usually the oral or genital areas). After a primary infection, the virus enters a latent state. Latent virus may or may not reactivate in the future. Typically, the primary infection is more severe than subsequent reactivations. However, not all individuals have symptoms during the primary infection and the first recognized symptoms may be in the setting of a reactivation. HSV infections are common. Seroprevalence of HSV-1 and HSV-2 in the United States

VHSV 62352

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(2005-2010) is 53.9% and 15.7%, respectively. (3) HSV-1 has historically been associated with oral lesions, but increasingly it is also a cause of genital herpes. Both HSV-1 and HSV-2 can cause severe CNS disease. In particular, HSV encephalitis in neonates is considered a medical emergency. Even with antiviral medication, there is significant morbidity and mortality associated with HSV encephalitis, especially in neonates. Fetal and neonatal HSV infections can be acquired in utero or at the time of delivery. The greatest risk for transmitting HSV is when the mother experiences a primary HSV infection, but there is also increased risk of transmission during periods of reactivation. Primary infection and reactivation may not be symptomatic, but nevertheless result in viral transmission to the fetus or newborn.

Diagnostic methods for HSV include routine viral culture, molecular testing by PCR, and serology. It is difficult to recover HSV from spinal fluid (CSF) specimens using viral culture, and a serologic response to HSV is not detectable immediately after infection. Detection of HSV by real-time PCR is now recognized as the most sensitive approach to diagnose HSV infection, especially CNS-associated HSV disease. However, it is still recommended to test neonates by viral culture when testing for potential congenital herpes by peripheral (eg, skin) swab, since PCR may detect low levels of HSV DNA or inactive virus in the absence of infectious viral particles. Infants younger than 4 weeks of age may have detectable HSV DNA on them that was shed by an infected mother, even in the absence of active HSV infection in the infant. On the other hand, a positive result by viral culture indicates the presence of live virus, suggesting active infection in the newborn.

**Useful For:** An aid in the diagnosis of congenital herpes simplex virus (HSV) infection in patients younger than 35 days old through the recovery of HSV using viral culture (shell-vial)

**Interpretation:** Recovery of herpes simplex virus (HSV) from clinical specimens supports the diagnosis of congenital HSV infection. A negative result by shell vial assay should be interpreted in the context of the patient’s clinical presentation and exposure history. Furthermore, testing by real-time PCR for this virus should be considered prior to ruling out HSV disease.

**Reference Values:**

No virus isolated

**Clinical References:**


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**LHSV 800143**

**Herpes Simplex Virus (HSV), Molecular Detection, PCR**

**Clinical Information:** Herpes simplex virus (HSV) types 1 and 2 are members of the Herpesviridae family, and produce infections that may range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV types 1 and 2 can differ significantly in their clinical manifestations and severity. HSV type 2 primarily causes urogenital infections and is found almost exclusively in adults. HSV type 1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. The diagnosis of HSV infections is routinely made based on clinical findings and supported by laboratory testing using PCR or viral culture.

**Useful For:** Aiding in the rapid diagnosis of herpes simplex virus (HSV) infections, including qualitative detection of HSV DNA in nonblood clinical specimens
Interpretation: This is a qualitative assay; results are reported either as negative or positive for herpes simplex virus (HSV) type 1 or HSV type 2, or HSV indeterminate. Detection of HSV DNA in clinical specimens supports the clinical diagnosis of infection due to the virus.

Reference Values:

Negative


Herpes Simplex Virus (HSV), Molecular Detection, PCR, Blood

Clinical Information: Herpes simplex virus (HSV) types 1 and 2 cause a variety of clinical syndromes. Anatomic sites infected include the skin, lips, oral cavity, eyes, genital tract, and central nervous system (CNS). Systemic disease may also occur, in which the virus may be detectable in the bloodstream. The detection of HSV-1 or HSV-2 from blood specimens may help support the diagnosis of disseminated disease associated with this virus.

Useful For: Aids in the rapid diagnosis of disseminated disease due to herpes simplex virus (HSV)

Qualitative detection of HSV DNA

Interpretation: This is a qualitative assay; results are reported either as negative or positive for herpes simplex virus (HSV) type 1 or HSV type 2. In a small number of cases (eg, <1%), HSV is detected but this assay may not be able to provide a definitive subtype (HSV-1 versus HSV-2). This is due to mutations in the region of the HSV genome to which the PCR probes bind. When this result is observed, the report will go out as "Indeterminate", which means that HSV DNA was detected, but the assay was unable to provide a specific subtype. Detection of HSV DNA in clinical specimens supports the clinical diagnosis of infection due to the virus.

Reference Values:

HERPES SIMPLEX VIRUS (HSV)-1

Negative

HERPES SIMPLEX VIRUS (HSV)-2

Negative

**Herpes Simplex Virus (HSV), Molecular Detection, PCR, Spinal Fluid**

**Clinical Information:** Herpes simplex virus (HSV)-1 and HSV-2 are members of the Alphaherpesviridae subfamily. HSV is an enveloped virus with a capsid containing viral DNA. Although HSV-1 and HSV-2 are closely related, the 2 viruses are serologically and genetically distinct.(1,2) HSV-1 and -2 are common causes of dermal and genital infections; however, in some cases, infection with HSV may result in central nervous system (CNS) disease that is considered a medical emergency. HSV infection of the CNS may result in encephalitis (more commonly associated with HSV-1) or meningitis (more commonly associated with HSV-2). Encephalitis is inflammation of the brain associated with clinical evidence of neurologic dysfunction. Of the pathogens reported to cause encephalitis, the majority are viruses.(3) In general, the most commonly identified etiologies in the United States are HSV, West Nile virus, and the enteroviruses, followed by other herpesviruses.(3) HSV causes about 5% to 10% of all encephalitis cases, and is one of the most common causes of identified sporadic encephalitis globally.(3) HSV encephalitis occurs in all ages, and during all seasons. HSV-1 encephalitis is more common in adults, and HSV-2 encephalitis is more common in neonates.(3) One study reported a neonatal herpes rate of 1 case per 3,200 live births in the United States.(4) Clinical features involved with HSV encephalitis include fever, hemicranial headache, language and behavioral abnormalities, memory impairment, and seizures.(3)

**Useful For:** Aids in the rapid diagnosis of herpes simplex virus (HSV)-1 and HSV-2 infections of the central nervous system

**Interpretation:** A positive result suggests the presence of herpes simplex virus (HSV)-1 and/or HSV-2 DNA in the cerebrospinal fluid (CSF) sample. A negative result suggests that HSV-1 and HSV-2 DNA are not present in the CSF sample. An invalid result points to the inability to determine presence or absence of HSV-1 or HSV-2 DNA in the CSF sample.

**Reference Values:**
Negative


**Herpes Simplex Virus 1 and 2, Qualitative PCR, Blood**

**Clinical Information:** Herpes simplex virus types 1 and 2 (HSV-1/2) are members of the Herpesviridae family, and produce infections that may range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV-1/2 can differ significantly in their clinical manifestations and severity. HSV-2 primarily causes urogenital infections and is found most often in adults. HSV-1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. In certain cases, the virus may disseminate and involve multiple organ systems, including the central nervous system. The diagnosis of HSV infections is routinely made based on clinical findings and supported by laboratory testing using polymerase chain reaction (PCR) or viral culture.
**Useful For:** Direct detection and differentiation of HSV-1 and HSV-2 DNA in whole blood specimens from symptomatic patients who are suspected to have disseminated disease. Aids in diagnosis of HSV infection in symptomatic patients. This test is not intended to be used for prenatal screenings.

**Interpretation:** This is a qualitative assay; results are reported either as negative or positive for herpes simplex virus (HSV) type 1 or HSV type 2 nucleic acid. Detection of HSV DNA in clinical specimens supports the clinical diagnosis of infection due to the virus.

**Reference Values:**

| HERPES SIMPLEX VIRUS (HSV)-1 | Negative |
| HERPES SIMPLEX VIRUS (HSV)-2 | Negative |

**Clinical References:**

**HERPES SIMPLEX VIRUS (HSV)-1**

**HERPES SIMPLEX VIRUS (HSV)-2**

**HERPES SIMPLEX VIRUS (HSV)-1**

**HERPES SIMPLEX VIRUS (HSV)-2**

**Clinical Information:** Herpes simplex virus types 1 and 2 (HSV-1/2) are members of the Herpesviridae family, and produce infections that may range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV-1 and -2 can differ significantly in their clinical manifestations and severity. HSV-2 primarily causes urogenital infections and is found most often in adults. HSV-1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. The diagnosis of HSV infections is routinely made based on clinical findings and supported by laboratory testing using polymerase chain reaction (PCR) or viral culture.

**Useful For:** Direct detection and differentiation of HSV-1 and HSV-2 DNA in various specimen types from symptomatic patients. Aids in diagnosis of HSV infection in symptomatic patients. This test is not intended to be used for prenatal screening.

**Interpretation:** This is a qualitative assay; results are reported either as negative or positive for herpes simplex virus (HSV) type 1 or HSV type 2 nucleic acid. Detection of HSV DNA in clinical specimens supports the clinical diagnosis of infection due to the virus.

**Reference Values:**

| HERPES SIMPLEX VIRUS (HSV)-1 | Negative |
| HERPES SIMPLEX VIRUS (HSV)-2 | Negative |

**Clinical References:**
Herpes Simplex Virus, I and II (HSV I and II) Immunostain, Technical Component Only

**Clinical Information:** Immunoperoxidase staining for herpes simplex virus (HSV) I and II produces nuclear and granular cytoplasmic staining of virus infected cells. HSV I and II are part of the herpes virus family that also includes Epstein Barr virus, herpes zoster, and cytomegalovirus. HSV are among the most common infectious agents of man and usually are transmitted through close personal contact. The manifestations of infection can be localized (oral lesions HSV I; genital lesions HSV II), or can cause life-threatening systemic infection in immunocompromised patients.

**Useful For:** Aids in the identification of herpes simplex virus I and II infection

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**Herpes Virus 6 DNA, Qualitative Real-Time PCR**

**Reference Values:**
Reference Range: Not Detected

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**Herpes Virus-6 DNA, Quantitative Real-Time PCR**

**Reference Values:**
<500 copies/mL

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**Herpesvirus 7 (HHV-7) DNA, Quantitative Real-Time PCR**

**Reference Values:**
Reference Range: <500 copies/mL
Herpesvirus 7 IgG and IgM Antibody Panel, IFA

Reference Values:
Reference Range:

<table>
<thead>
<tr>
<th></th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
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<td>&lt;1:320</td>
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<tr>
<td>IgM</td>
<td>&lt;1:20</td>
</tr>
</tbody>
</table>

Human Herpesvirus 7 (HHV-7), a close relative of HHV-6, is found in >85% of the population, with transmission occurring in early childhood. Like HHV-6, HHV-7 is a cause of exanthem subitum (roseola infantum). Due to the ubiquitous nature of HHV-7 infection, >80% of individuals in the general population exhibit HHV-7 IgG titers >or=1:20; however, only 5% of these individuals exhibit titers >1:320. Thus, HHV-7 IgG titers > 1:320 are suggestive of recent HHV-7 infection. Detection of HHV-7 specific IgM is also indicative of recent infection.

Herpesvirus 8 (HHV-8) DNA, Quantitative Real-Time PCR

Reference Values:
Reference Range: <1000 copies/mL

Herring, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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</tr>
<tr>
<td>1</td>
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<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
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**FHEXA**

**Hexagonal Phospholipid Neutralization**

**Reference Values:**

All ages: 0-11 sec

This is a qualitative assay and is therefore reported as positive for lupus anticoagulant or negative. The quantitative value is provided as an aid in diagnosis.

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**HEXAI**

**Hexahydrophthalic Anhydride, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<th>Class</th>
<th>IgE kU/L</th>
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</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<td>Negative</td>
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<td>Equivocal</td>
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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
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<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
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</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
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**Hexosaminidase A (MUGS), Serum**

**Clinical Information:** Tay-Sachs and Sandhoff diseases are lysosomal storage disorders, also referred to as GM2 gangliosidoses, caused by deficiencies of the enzymes hexosaminidase A and hexosaminidase B, respectively. These isoenzymes are dimers that differ in their subunit composition. Hexosaminidase A is a heterodimer composed of 1 alpha and 1 beta subunit (alpha-beta), while hexosaminidase B is a homodimer composed of 2 beta subunits (beta-beta). The defective lysosomal degradation and the excessive accumulation of GM2 ganglioside and related glycolipids results in the development of the clinical symptomology observed in Tay-Sachs and Sandhoff diseases. Tay-Sachs disease is an autosomal recessive condition resulting from 2 mutations in the HEXA gene, which encodes for the alpha subunit of hexosaminidase. Individuals with Tay-Sachs disease have a deficiency of hexosaminidase A. Variability is observed with respect to age of onset and clinical symptoms. The acute infantile form typically presents with progressive motor deterioration beginning at 3 to 6 months of age. Patients exhibit weakness, hypotonia, and decreasing attentiveness. Motor skills learned previously, such as crawling or sitting alone, are nearly always lost by age 1. Other symptoms include rapid diminishing of vision, seizures, macrocephaly due to cerebral gliosis, and a characteristic cherry-red spot in the retina. Affected individuals typically do not survive past age 5. The juvenile or subacute form of Tay-Sachs disease often presents between ages 2 and 10 with ataxia and clumsiness. Patients develop difficulties with speech and cognition. Neurologic features progressively worsen and death is typically 2 to 4 years later. Disease progression is slower in patients with chronic or adult-onset Tay-Sachs disease. Early signs and symptoms may be subtle and nonspecific, involving muscle or neurologic findings, often resulting in initial misdiagnoses. Affected individuals may exhibit abnormalities of gait and posture, spasticity, dysarthria (loss of speech), and progressive muscle wasting and weakness. Cognitive impairment, dementia, or psychiatric findings are observed in some patients. Significant clinical variability exists between and within families. The carrier frequency of Tay-Sachs disease is increased in certain groups including individuals of Ashkenazi Jewish, Celtic, and French Canadian ancestry. A common cause of false-positive carrier screening by enzyme analysis, particularly among individuals of non-Ashkenazi Jewish descent, is due to the presence of pseudodeficiency alleles. Such sequence variations are not associated with disease, but result in the production of a hexosaminidase A enzyme with decreased activity towards the artificial substrate typically used in the enzyme assay. The recommended testing strategy is to order NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex, which begins with enzyme analysis and when the percent of hexosaminidase A enzyme is low, reflexes to the molecular panel that includes the most common mutations observed in these high-risk populations and 2 common pseudodeficiency alleles. Sandhoff disease (not detected by MUGS) is an autosomal recessive condition resulting from 2 mutations in the HEXB gene, which encodes for the beta subunit of hexosaminidase. Individuals with Sandhoff disease have deficiencies in both hexosaminidase A and hexosaminidase B. Phenotypically, patients with Sandhoff disease present with features very similar to Tay-Sachs disease including variability in age of onset and severity. Enzyme analysis is generally required to distinguish between the 2 disorders. Unlike Tay-Sachs disease, Sandhoff disease does not have an increased carrier frequency in any specific population. Testing for Tay-Sachs and Sandhoff diseases occurs by analysis of hexosaminidase A, a heat-labile enzyme, and total hexosaminidase (hexosaminidase A plus hexosaminidase B). When testing the enzyme, an artificial substrate is most commonly used. The total hexosaminidase is quantified. Following this, heat inactivation of hexosaminidase A occurs with a second measurement of the total enzyme level. From this, the percent hexosaminidase A is calculated. Biochemically, Tay-Sachs disease is characterized by normal total hexosaminidase with a very low percent hexosaminidase A. Carriers of Tay-Sachs disease are asymptomatic, but have intermediate percent hexosaminidase A in serum and leukocytes. Follow-up molecular testing is recommended for all individuals with enzyme results in the carrier or possible carrier ranges to differentiate carriers of a pseudodeficiency allele from those with a disease-causing mutation. In addition, this allows for the facilitation of prenatal diagnosis for at-risk pregnancies. A very small group of patients affected with Tay-Sachs disease have mutations referred to as the B1 variant. In the presence of an artificial substrate,
the B1 variant allows for a heterodimer formation of hexosaminidase A and exhibits activity. However, in vivo the B1 variant hexosaminidase A is inactive on the natural substrate. Thus, with the artificial substrate, these patients appear to be unaffected. Individuals with the B1 variant of Tay-Sachs disease must be distinguished using a natural substrate assay (MUGS / Hexosaminidase A [MUGS], Serum). Clinically, patients with at least one B1 variant typically become symptomatic beyond the infantile period. This testing should be considered if one of the other assays indicates normal, indeterminate, or carrier results and the suspicion of Tay-Sachs disease remains high. Hexosaminidase testing using the artificial substrate provides an indirect assay for Sandhoff disease. Affected individuals exhibit very low total hexosaminidase with a disproportionately high percent hexosaminidase A due to alpha subunit homodimer formation. Carriers of Sandhoff disease are asymptomatic but have intermediate levels of total hexosaminidase with a high percent hexosaminidase A in serum, leukocytes, and cultured fibroblasts. However, not all individuals with this pattern are true carriers of Sandhoff disease and follow-up molecular testing is recommended. In addition, molecular analysis allows for the facilitation of prenatal diagnosis for at-risk pregnancies. Testing hexosaminidase using the natural substrate (MUGS) does not identify homozygotes or heterozygotes for Sandhoff disease.

**Useful For:** Second-order test for diagnosing the B1 variant of Tay-Sachs disease

**Interpretation:** Interpretation is provided with report. The B1 mutation results in depressed Hex A isoenzyme as assayed by MUGS / Hexosaminidase A (MUGS), Serum using the natural substrate, 4-MUGS; whereas it reacts normally to the artificial substrate 4-MUG as assayed by NAGW / Hexosaminidase A and Total Hexosaminidase, Leukocytes; NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex; and NAGS / Hexosaminidase A and Total Hexosaminidase, Serum. For carrier testing only, follow-up testing using leukocytes is recommended for indeterminate results.

**Reference Values:**
1.23-2.59 U/L (normal)
1.16-1.22 U/L (indeterminate)
0.58-1.15 U/L (carrier)

**Clinical References:**

**Hexosaminidase A and Total Hexosaminidase, Leukocytes**

**Clinical Information:** Tay-Sachs and Sandhoff diseases are lysosomal storage disorders, also referred to as GM2 gangliosidoses, caused by deficiencies of the enzymes hexosaminidase A and hexosaminidase B, respectively. These isoenzymes are dimers that differ in their subunit composition. Hexosaminidase A is a heterodimer composed of 1 alpha and 1 beta subunit (alpha-beta), while hexosaminidase B is a homodimer composed of 2 beta subunits (beta-beta). The defective lysosomal degradation and the excessive accumulation of GM2 ganglioside and related glycolipids results in the development of the clinical symptomology observed in Tay-Sachs and Sandhoff diseases. Tay-Sachs disease is an autosomal recessive condition resulting from 2 mutations in HEXA, which encodes for the alpha subunit of hexosaminidase. Individuals with Tay-Sachs disease have a deficiency of hexosaminidase A. Variability is observed with respect to age of onset and clinical symptoms. The acute infantile form typically presents with progressive motor deterioration beginning at 3 to 6 months of age. Patients exhibit weakness, hypotonia, and decreasing attentiveness. Motor skills learned previously, such as crawling or sitting alone, are nearly always lost by age 1. Other symptoms include rapid diminishing of vision, seizures, macrocephaly due to cerebral gliosis, and the characteristic...
cherry-red spot in the retina. Affected individuals typically do not survive past age 5. The juvenile or subacute form of Tay-Sachs disease often presents between 2 and 10 years with ataxia and clumsiness. Patients develop difficulties with speech and cognition. Neurologic features progressively worsen and death is typically 2 to 4 years later. Disease progression is slower in patients with chronic or adult-onset Tay-Sachs disease. Early signs and symptoms may be subtle and nonspecific, involving muscle and/or neurologic findings, often resulting in initial misdiagnoses. Affected individuals may exhibit abnormalities of gait and posture, spasticity, dysarthria (loss of speech), and progressive muscle wasting and weakness. Cognitive impairment, dementia, or psychiatric findings are observed in some patients. Significant clinical variability exists both between and within families. The carrier frequency of Tay-Sachs disease is increased in certain groups including individuals of Ashkenazi Jewish, Celtic, and French Canadian ancestry. A common cause of false-positive carrier screening by enzyme analysis, particularly among individuals of non-Ashkenazi Jewish descent, is due to the presence of pseudodeficiency alleles. Such sequence variations are not associated with disease, but result in the production of a hexosaminidase A enzyme with decreased activity towards the artificial substrate typically used in the enzyme assay. The recommended testing strategy is to order NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex, which begins with enzyme analysis and when the percent of hexosaminidase A enzyme is low, reflexes to the molecular panel which includes the most common mutations observed in these high-risk populations and 2 common pseudodeficiency alleles. Sandhoff disease is an autosomal recessive condition resulting from 2 mutations in HEXB, which encodes for the beta subunit of hexosaminidase. Individuals with Sandhoff disease have deficiencies in both hexosaminidase A and hexosaminidase B. Phenotypically, patients with Sandhoff disease present with features very similar to Tay-Sachs disease including variability in age of onset and severity. Enzyme analysis is generally required to distinguish between the 2 disorders. Unlike Tay-Sachs disease, Sandhoff disease does not have an increased carrier frequency in any specific population. Testing for Tay-Sachs and Sandhoff diseases occurs by analysis of hexosaminidase A, a heat-labile enzyme, and total hexosaminidase (hexosaminidase A plus hexosaminidase B). When testing the enzyme, an artificial substrate is most commonly used. The total hexosaminidase is quantified. Following this, heat inactivation of hexosaminidase A occurs with a second measurement of the total enzyme level. From this, the percent hexosaminidase A is calculated. Biochemically, Tay-Sachs disease is characterized by normal total hexosaminidase with a very low percent hexosaminidase A. Carriers of Tay-Sachs disease are asymptomatic, but have intermediate percent hexosaminidase A in serum and leukocytes. Follow-up molecular testing is recommended for all individuals with enzyme results in the carrier or possible carrier ranges to differentiate carriers of a pseudodeficiency allele from those with a disease-causing mutation. In addition, this allows for the facilitation of prenatal diagnosis for at-risk pregnancies. A very small group of patients affected with Tay-Sachs disease have mutations referred to as the B1 variant. In the presence of an artificial substrate, the B1 variant allows for a heterodimer formation of hexosaminidase A and exhibits activity. However, in vivo the B1 variant hexosaminidase A is inactive on the natural substrate. Thus, with the artificial substrate, these patients appear to be unaffected. Individuals with the B1 variant of Tay-Sachs disease must be distinguished using a natural substrate assay (MUGS / Hexosaminidase A [MUGS], Serum). Clinically, patients with at least one B1 variant typically become asymptomatic beyond the infantile period. This testing should be considered if one of the other assays indicates normal, indeterminate, or carrier results and the suspicion of Tay-Sachs disease remains high. Hexosaminidase testing using the artificial substrate provides an indirect assay for Sandhoff disease. Affected individuals exhibit very low total hexosaminidase with a disproportionately high percent hexosaminidase A due to alpha subunit homodimer formation. Carriers of Sandhoff disease are asymptomatic but have intermediate levels of total hexosaminidase with high percent hexosaminidase A in serum and leukocytes. However, not all individuals with this pattern are true carriers of Sandhoff disease and follow-up molecular testing is recommended. In addition, molecular analysis allows for the facilitation of prenatal diagnosis for at-risk pregnancies. Testing hexosaminidase using the natural substrate does not identify homozygotes or heterozygotes for Sandhoff disease. For additional testing options for Tay-Sachs and Sandhoff disease, see NAGW / Hexosaminidase A and Total Hexosaminidase, Leukocytes (Tay-Sachs disease only) and NAGS / Hexosaminidase A and Total Hexosaminidase, Serum (Tay-Sachs and Sandhoff diseases (not appropriate for Sandhoff detection in females who are pregnant or receiving hormonal contraception).

**Useful For:** Carrier detection and diagnosis of Tay-Sachs disease Carrier detection and diagnosis of Sandhoff disease
**Interpretation:** Interpretation is provided with report. Hexosaminidase A usually composes more than 62% of the total hexosaminidase activity in leukocytes (normal =63%-75% A). In leukocytes, the percent Hex A is used in determining whether an individual is a carrier of or affected with Tay-Sachs disease: -63% to 75% hexosaminidase A is normal (noncarrier) -58% to 62% hexosaminidase A is indeterminate (molecular testing recommended to discern carriers from non-carriers and to allow for prenatal diagnosis if desired) -less than 58% hexosaminidase A is a carrier (molecular testing recommended to discern disease-causing mutations from pseudodeficiency alleles and to allow for prenatal diagnosis, if desired) -less than 20% hexosaminidase A is consistent with a diagnosis of Tay-Sachs disease In leukocytes, the total hexosaminidase in combination with the percent hexosaminidase A aids in determining whether an individual is at-risk to be a carrier of or is affected with Sandhoff disease: -greater than or equal to 76% hexosaminidase A is suggestive of a Sandhoff carrier, when the total hexosaminidase is depressed -Total hexosaminidase activity near zero with nearly 100% hexosaminidase A is consistent with Sandhoff disease

**Reference Values:**

<table>
<thead>
<tr>
<th>Test</th>
<th>&lt; or =15 years</th>
<th>&gt; or =16 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEXOSAMINIDASE TOTAL</td>
<td>&lt;20 nmol/min/mg</td>
<td>16.4-36.2 nmol/min/mg</td>
</tr>
<tr>
<td>HEXOSAMINIDASE PERCENT A</td>
<td>20-80% of total</td>
<td>63-75% of total</td>
</tr>
</tbody>
</table>

**Clinical References:**

**Hexosaminidase A and Total Hexosaminidase, Serum**

**Clinical Information:** Tay-Sachs and Sandhoff diseases are lysosomal storage disorders, also referred to as GM2 gangliosidoses, caused by deficiencies of the enzymes hexosaminidase A and hexosaminidase B, respectively. These isoenzymes are dimers that differ in their subunit composition. Hexosaminidase A is a heterodimer composed of 1 alpha and 1 beta subunit (alpha-beta), while hexosaminidase B is a homodimer composed of 2 beta subunits (beta-beta). The defective lysosomal degradation and the excessive accumulation of GM2 ganglioside and related glycolipids results in the development of the clinical symptomology observed in Tay-Sachs and Sandhoff diseases. Tay-Sachs disease is an autosomal recessive condition resulting from 2 mutations in the HEXA gene, which encodes for the alpha subunit of hexosaminidase. Individuals with Tay-Sachs disease have a deficiency of hexosaminidase A. Variability is observed with respect to age of onset and clinical symptoms. The acute infantile form typically presents with progressive motor deterioration beginning at 3 to 6 months of age. Patients exhibit weakness, hypotonia, and decreasing attentiveness. Motor skills learned previously, such as crawling or sitting alone, are nearly always lost by age 1. Other symptoms include rapid diminishing of vision, seizures, macrocephaly due to cerebral gliosis, and the characteristic cherry-red spot in the retina. Affected individuals typically do not survive past age 5. The juvenile or subacute form of Tay-Sachs disease often presents between 2 and 10 years with ataxia and clumsiness.
Patients develop difficulties with speech and cognition. Neurologic features progressively worsen and death is typically 2 to 4 years later. Disease progression is slower in patients with chronic or adult-onset Tay-Sachs disease. Early signs and symptoms may be subtle and nonspecific, involving muscle and/or neurologic findings, often resulting in initial misdiagnoses. Affected individuals may exhibit abnormalities of gait and posture, spasticity, dysarthria (loss of speech), and progressive muscle wasting and weakness. Cognitive impairment, dementia, or psychiatric findings are observed in some patients. Significant clinical variability exists both between and within families. The carrier frequency of Tay-Sachs disease is increased in certain groups including individuals of Ashkenazi Jewish, Celtic, and French Canadian ancestry. A common cause of false-positive carrier screening by enzyme analysis, particularly among individuals of non-Ashkenazi Jewish descent, is due to the presence of pseudodeficiency alleles. Such sequence variations are not associated with disease, but result in the production of a hexosaminidase A enzyme with decreased activity towards the artificial substrate typically used in the enzyme assay. The recommended testing strategy is to order NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex, which begins with enzyme analysis and when the percent of hexosaminidase A enzyme is low, reflexes to the molecular panel which includes the most common mutations observed in these high-risk populations and 2 common pseudodeficiency alleles. Sandhoff disease is an autosomal recessive condition resulting from 2 mutations in the HEXB gene, which encodes for the beta subunit of hexosaminidase. Individuals with Sandhoff disease have deficiencies in both hexosaminidase A and hexosaminidase B. Phenotypically, patients with Sandhoff disease present with features very similar to Tay-Sachs disease including variability in age of onset and severity. Enzyme analysis is generally required to distinguish between the 2 disorders. Unlike Tay-Sachs disease, Sandhoff disease does not have an increased carrier frequency in any specific population. Testing for Tay-Sachs and Sandhoff diseases occurs by analysis of hexosaminidase A, a heat-labile enzyme, and total hexosaminidase (hexosaminidase A plus hexosaminidase B). When testing the enzyme, an artificial substrate is most commonly used. The total hexosaminidase is quantified. Following this, heat inactivation of hexosaminidase A occurs with a second measurement of the total enzyme level. From this, the percent hexosaminidase A is calculated. Biochemically, Tay-Sachs disease is characterized by normal total hexosaminidase with a very low percent hexosaminidase A. Carriers of Tay-Sachs disease are asymptomatic, but have intermediate percent hexosaminidase A in serum and leukocytes. Follow-up molecular testing is recommended for all individuals with enzyme results in the carrier or possible carrier ranges to differentiate carriers of a pseudodeficiency allele from those with a disease-causing mutation. In addition, this allows for the facilitation of prenatal diagnosis for at-risk pregnancies. A very small group of patients affected with Tay-Sachs disease have mutations referred to as the B1 variant. In the presence of an artificial substrate, the B1 variant allows for a heterodimer formation of hexosaminidase A and exhibits activity. However, in vivo the B1 variant hexosaminidase A is inactive on the natural substrate. Thus, with the artificial substrate, these patients appear to be unaffected. Individuals with the B1 variant of Tay-Sachs disease must be distinguished using a natural substrate assay (MUGS / Hexosaminidase A [MUGS], Serum). Clinically, patients with at least one B1 variant typically become symptomatic beyond the infantile period. This testing should be considered if one of the other assays indicates normal, indeterminate, or carrier results and the suspicion of Tay-Sachs disease remains high. Hexosaminidase testing using the artificial substrate provides an indirect assay for Sandhoff disease. Affected individuals exhibit very low total hexosaminidase with a disproportionately high percent hexosaminidase A due to alpha subunit homodimer formation. Carriers of Sandhoff disease are asymptomatic but have intermediate levels of total hexosaminidase with high percent hexosaminidase A in serum and leukocytes. However, not all individuals with this pattern are true carriers of Sandhoff disease and follow-up molecular testing is recommended. In addition, molecular analysis allows for the facilitation of prenatal diagnosis for at-risk pregnancies. Testing hexosaminidase using the natural substrate does not identify homozygotes or heterozygotes for Sandhoff disease.

**Useful For:** Recommended test for carrier detection and diagnosis of Sandhoff disease (except in instances of females who are pregnant or receiving hormonal contraception) Carrier detection and diagnosis of Tay-Sachs disease

**Interpretation:** Interpretation is provided with report.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 15 years</td>
<td>&gt; or =20 nmol/min/mL</td>
</tr>
<tr>
<td>&gt; or =16 years</td>
<td>10.4-23.8 nmol/min/mL</td>
</tr>
</tbody>
</table>
HEXOSAMINIDASE PERCENT A, S
< or =15 years: 20-90%
> or =16 years: 56-80%


Hexosaminidase A and Total, Leukocytes/Molecular Reflex

Clinical Information: Tay-Sachs and Sandhoff diseases are lysosomal storage disorders, also referred to as GM2 gangliosidoses, caused by deficiencies of the enzymes hexosaminidase A and hexosaminidase B, respectively. These isoenzymes are dimers that differ in their subunit composition. Hexosaminidase A is a heterodimer composed of 1 alpha and 1 beta subunit (alpha-beta), while hexosaminidase B is a homodimer composed of 2 beta subunits (beta-beta). The defective lysosomal degradation and the excessive accumulation of GM2 ganglioside and related glycolipids results in the development of the clinical symptomology observed in Tay-Sachs and Sandhoff diseases. Tay-Sachs disease is an autosomal recessive condition resulting from 2 mutations in HEXA, which encodes for the alpha subunit of hexosaminidase. Individuals with Tay-Sachs disease have a deficiency of hexosaminidase A. Variability is observed with respect to age of onset and clinical symptoms. The acute infantile form typically presents with progressive motor deterioration beginning at 3 to 6 months of age. Patients exhibit weakness, hypotonia, and decreasing attentiveness. Motor skills learned previously, such as crawling or sitting alone, are nearly always lost by age 1. Other symptoms include rapid diminishing of vision, seizures, macrocephaly due to cerebral gliosis, and the characteristic cherry-red spot in the retina. Affected individuals typically do not survive past age 5. The juvenile or subacute form of Tay-Sachs disease often presents between 2 and 10 years with ataxia and clumsiness. Patients develop difficulties with speech and cognition. Neurologic features progressively worsen and death is typically 2 to 4 years later. Disease progression is slower in patients with chronic or adult-onset Tay-Sachs disease. Early signs and symptoms may be subtle and nonspecific, involving muscle and/or neurologic findings, often resulting in initial misdiagnoses. Affected individuals may exhibit abnormalities of gait and posture, spasticity, dystonia (loss of speech), and progressive muscle wasting and weakness. Cognitive impairment, dementia, or psychiatric findings are observed in some patients. Significant clinical variability exists both between and within families. The carrier frequency of Tay-Sachs disease is increased in certain groups including individuals of Ashkenazi Jewish, Celtic, and French Canadian ancestry. A common cause of false-positive carrier screening by enzyme analysis, particularly among individuals of non-Ashkenazi Jewish descent, is due to the presence of pseudodeficiency alleles. Such sequence variations are not associated with disease, but result in the production of a hexosaminidase A enzyme with decreased activity towards the artificial substrate typically used in the enzyme assay. The recommended testing strategy is to order NAGR / Hexosaminidase A and Total, Leukocytes/Molecular Reflex, which begins with enzyme analysis and when the percent of hexosaminidase A enzyme is low, reflexes to the molecular panel which includes the most common mutations observed in these high-risk populations and 2 common pseudodeficiency alleles. Sandhoff disease is an autosomal recessive condition resulting from 2 mutations in HEXB, which encodes for the beta subunit of hexosaminidase. Individuals with Sandhoff disease have deficiencies in both hexosaminidase A and hexosaminidase B. Phenotypically, patients with Sandhoff disease present with features very similar to Tay-Sachs disease including variability in age of onset and severity. Enzyme analysis is generally required to distinguish between the 2 disorders. Unlike Tay-Sachs disease, Sandhoff disease does not have an increased carrier frequency in any specific population. Testing for Tay-Sachs and Sandhoff diseases occurs by analysis of hexosaminidase A, a
heat-labile enzyme, and total hexosaminidase (hexosaminidase A plus hexosaminidase B). When testing
the enzyme, an artificial substrate is most commonly used. The total hexosaminidase is quantified.
Following this, heat inactivation of hexosaminidase A occurs with a second measurement of the total
enzyme level. From this, the percent hexosaminidase A is calculated. Biochemically, Tay-Sachs disease
is characterized by normal total hexosaminidase with a very low percent hexosaminidase A. Carriers of
Tay-Sachs disease are asymptomatic, but have intermediate percent hexosaminidase A in serum and
leukocytes. Follow-up molecular testing is recommended for all individuals with enzyme results in the
carrier or possible carrier ranges to differentiate carriers of a pseudodeficiency allele from those with a
disease-causing mutation. In addition, this allows for the facilitation of prenatal diagnosis for at-risk
pregnancies. A very small group of patients affected with Tay-Sachs disease have mutations referred to
as the B1 variant. In the presence of an artificial substrate, the B1 variant allows for a heterodimer
formation of hexosaminidase A and exhibits activity. However, in vivo the B1 variant hexosaminidase
A is inactive on the natural substrate. Thus, with the artificial substrate, these patients appear to be
unaffected. Individuals with the B1 variant of Tay-Sachs disease must be distinguished using a natural
substrate assay (MUGS / Hexosaminidase A [MUGS], Serum). Clinically, patients with at least one B1
variant typically become symptomatic beyond the infantile period. This testing should be considered if
one of the other assays indicates normal, indeterminate, or carrier results and the suspicion of Tay-Sachs
disease remains high. Hexosaminidase testing using the artificial substrate provides an indirect assay for
Sandhoff disease. Affected individuals exhibit very low total hexosaminidase with a disproportionately
high percent hexosaminidase A due to alpha subunit homodimer formation. Carriers of Sandhoff disease
are asymptomatic but have intermediate levels of total hexosaminidase with high percent
hexosaminidase A in serum and leukocytes. However, not all individuals with this pattern are true
 carriers of Sandhoff disease and follow-up molecular testing is recommended. In addition, molecular
analysis allows for the facilitation of prenatal diagnosis for at-risk pregnancies. Testing hexosaminidase
using the natural substrate does not identify homozygotes or heterozygotes for Sandhoff disease. For
additional testing options for Tay-Sachs and Sandhoff disease, see NAGW / Hexosaminidase A and
Total Hexosaminidase, Leukocytes (Tay-Sachs disease only) and NAGS / Hexosaminidase A and Total
Hexosaminidase, Serum (Tay-Sachs and Sandhoff diseases (not appropriate for Sandhoff detection in
females who are pregnant or receiving hormonal contraception).

Useful For: Carrier detection and diagnosis of Tay-Sachs disease Recommended test for carrier
detection of Tay-Sachs disease Carrier detection and diagnosis of Sandhoff disease

Interpretation: Interpretation is provided with report. Hexosaminidase A usually composes greater
than 62% of the total hexosaminidase activity in leukocytes (normal = 63%-75% A). In leukocytes, the
percent Hex A is used in determining whether an individual is a carrier of or affected with Tay-Sachs
disease: -63% to 75% hexosaminidase A is normal (noncarrier) -58% to 62% hexosaminidase A is
indeterminate (molecular testing recommended to discern carriers from non-carriers and to allow for
prenatal diagnosis if desired) -less than 58% hexosaminidase A is a carrier (molecular testing
recommended to discern disease-causing mutations from pseudodeficiency alleles and to allow for
prenatal diagnosis if desired) -less than 20% hexosaminidase A is consistent with a diagnosis of
Tay-Sachs disease. In leukocytes, the total hexosaminidase in combination with the percent
hexosaminidase A aids in determining whether an individual is at-risk to be a carrier of or is affected with
Sandhoff disease: -greater than or equal to 76% hexosaminidase A is suggestive of a Sandhoff carrier,
when the total hexosaminidase is depressed -Total hexosaminidase activity near zero with nearly 100%
hexosaminidase A is consistent with Sandhoff disease

Reference Values:
HEXOSAMINIDASE TOTAL
< or =15 years: > or =20 nmol/min/mg
> or =16 years: 16.4-36.2 nmol/min/mg

HEXOSAMINIDASE PERCENT A
< or =15 years: 20-80% of total
> or =16 years: 63-75% of total

carriers of Tay-Sachs disease among Ashkenazi Jews-A comparison of DNA-based and enzyme-based

**FSHAG 57950**

**Hickory Shagbark (Carya ovata) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

**HMGA 70460**

**High Mobility Group A2 (HMGA2) Immunostain, Technical Component Only**

**Clinical Information:** High mobility group (HMG) proteins are nonhistone chromatin factors expressed during embryonic development that function to regulate transcription and cellular differentiation. When expression of HMGA2 is deregulated in cells of adult tissues, this oncofetal protein promotes neoplastic transformation. Abnormal HMGA2 expression has been observed in a wide variety of neoplasms, including uterine leiomyomas, ovarian serous carcinomas, lipomatous tumors, lymphangiomyomatosis, and pancreatic carcinomas. Normal spermatids express HMGA2. This immunostain may be useful in the differential diagnosis of lower genital tract mesenchymal tumors, showing positivity in the majority of aggressive angiomyxomas.

**Useful For:** An aid in the identification of abnormal expression of the high mobility group (HMG) protein HMGA2

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Hippuric Acid, Urine

Reference Values:
Reporting limit determined each analysis

Creatinine (mg/L):
U.S. Population (10th â€“ 90th percentiles, median)
All participants:
335 - 2370 mg/L, median: 1180 (n=22,245)
Males:
495 - 2540 mg/L, median: 1370 (n=10,610)
Females:
273 - 2170 mg/L, median 994 (n=11,635)

Hippuric Acid (g/L)
Synonym(s): Hippurate; n-Benzoylglycine
Normal for unexposed populations is generally less than 1.6 g/L.

Hippuric Acid (Creatinine corrected) (g/g Creat)
Synonym(s): Hippurate; n-Benzoylglycine
Normal for unexposed populations is generally less than 1.5 g/g creatinine.

Specific Gravity Confirmation
Physiologic range: 1.010 - 1.030

Histamine Plasma

Reference Values:
<1.0 ng/mL

Histamine, 24-Hour Urine

Clinical Information: Histamine is a mediator of the allergic response. Histamine release causes itching, flushing, hives, vomiting, syncope, and even shock. In addition, some patients with gastric carcinoids may exhibit high concentrations of histamine.

Reference Values:
Histamine, 24-hour Urine: 0.006 – 0.131 mg/24 h

Creatinine, 24-Hour Urine

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>g/24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-8</td>
<td>0.11 - 0.68</td>
</tr>
<tr>
<td>9-12</td>
<td>0.17 - 1.41</td>
</tr>
<tr>
<td>13-17</td>
<td>0.29 - 1.87</td>
</tr>
<tr>
<td>Adults</td>
<td>0.63 - 2.50</td>
</tr>
</tbody>
</table>

Histamine, Whole Blood

Reference Values:
180 - 1800 nmol/L

Histone Autoantibodies, Serum
**Clinical Information:** Histones are the most basic protein components of chromatin and their structures are highly conserved in different species. Five classes of histones called H1, H2, H2b, H3, and H4 have been described and are characterized by their molecular weights, ranging from 11 to 23 kilodalton (kD), and their content of the basic amino acids lysine and arginine. Histone autoantibodies may react with any of the 5 classes of histones. (1,2) Autoantibodies to total histones are elicited by unknown mechanisms in patients treated with certain drugs, particularly procainamide, hydralazine, quinidine, alpha methyl dopa, penicillamine, and isoniazid. Those patients may have signs and symptoms that resemble systemic lupus erythematosus (SLE). This disorder is identified as drug-induced lupus. Testing for autoantibodies to total histones is useful for evaluating patients suspected of having drug-induced lupus. Such patients will usually have a positive test for histone autoantibodies and a negative test for autoantibodies to double stranded DNA (dsDNA). Patients with SLE have positive tests for both types of autoantibodies.

**Useful For:** Evaluating patients suspected of having drug-induced lupus

**Interpretation:** A positive result for histone autoantibodies with a negative result for autoantibodies to double-stranded DNA (anti-ds-DNA) is consistent with drug-induced lupus. A positive result for histone autoantibodies with a positive result for anti-dsDNA autoantibodies is consistent with systemic lupus erythematosus.

**Reference Values:**
- <1.0 Units (negative)
- 1.0-1.5 Units (borderline)
- >1.5 Units (positive)

Units are arbitrarily based on positive control serum.
Reference values apply to all ages.


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**Histone H3 K27M mutant (H3 K27M), Technical Component Only**

**Clinical Information:** Histone H3 K27M is a mutation in the H3F3A gene, encoding for histone H3.3. This mutation is characteristic of “diffuse midline glioma, H3 K27M-mutant,” a new entity in the classification of central nervous system tumors, which carries a poor prognosis. H3 K27M-mutant diffuse midline glioma occurs most commonly in young children but can less frequently occur in adults. The most common locations including brain stem, thalamus, and spinal cord. The term brain stem glioma and diffuse intrinsic pontine glioma (DIPG) were previously used to indicate tumors occurring in the brain stem and pons respectively.

**Useful For:** Identifying the presence of mutated H3 K27M protein

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**HISME 72127**

**Histone H3 Trimethyl K27 (H3 K27me[3]) Immunostain, Technical Component Only**

**Clinical Information:** Histone H3K27 trimethylation (H3K27me3) is a bivalent epigenetic regulator that silences or represses the gene. Evaluation of H3K27me3 immunohistochemical expression is a helpful biomarker in the diagnosis of diffuse midline gliomas H3 K27M-mutant, which most frequently occur in children and with less frequency in adults. These tumors typically occur along the midline and include intrinsic pontine gliomas (DIPG), thalamic and spinal cord diffuse gliomas. H3 K27M mutations lead to global reduction in H3K27me3 and result in H3K27me3 loss of expression. Histologic mimics can be distinguishable from malignant peripheral nerve sheath tumors that show H3K27me3 loss of expression.

**Useful For:** Diagnosis of malignant peripheral nerve sheath tumors and diffuse midline gliomas H3 K27M-mutant

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**SHSTO 26692**

**Histoplasma Antibody, Serum**

**Clinical Information:** Histoplasma capsulatum is a soil saprophyte that grows well in soil enriched with bird droppings. The usual disease is self-limited, affects the lungs, and is asymptomatic. Chronic cavitary pulmonary disease, disseminated disease, and meningitis may occur and can be fatal, especially in young children and in immunosuppressed patients.

**Useful For:** Aiding in the diagnosis of active histoplasmosis in serum specimens

**Interpretation:** Complement fixation (CF) titers of 1:32 or higher indicate active disease. A rising CF titer is associated with progressive infection. Positive immunodiffusion test results supplement findings of the CF test. The simultaneous appearance of both H and M precipitin bands indicates active histoplasmosis. The M precipitin band alone indicates early or chronic disease or a recent histoplasmosis skin test. Patients infected with Histoplasma capsulatum demonstrate a serum antibody with a rising titer within 6 weeks of infection. A rising titer is associated with progressive infection. Specific antibody persists for a few weeks to a year, regardless of clinical improvement.
Histoplasma Antibody, Spinal Fluid

**Clinical Information:** Histoplasma capsulatum is a soil saprophyte that grows well in soil enriched with bird droppings. The usual disease is self-limited, affects the lungs, and is asymptomatic. Chronic cavitary pulmonary disease, disseminated disease, and meningitis may occur and can be fatal, especially in young children and immunosuppressed patients.

**Useful For:** Aiding in the diagnosis of Histoplasma meningitis in spinal fluid specimens

**Interpretation:** Any positive serologic result in spinal fluid is significant. Simultaneous appearance of the H and M precipitin bands indicates active histoplasmosis. The M band alone indicates active or chronic disease or a recent skin test for histoplasmosis.

**Reference Values:**

MYCELIAL BY COMPLEMENT FIXATION (CF)
Negative (positives reported as titer)

YEAST BY CF
Negative (positives reported as titer)

ANTIBODY BY IMMUNODIFFUSION
Negative (positives reported as band present)


Histoplasma Antigen, Urine

**Clinical Information:** Histoplasma capsulatum is a dimorphic fungus endemic to the Midwest United States, particularly along the Mississippi River and Ohio River valleys. Infection occurs following inhalation of fungal microconidia and subsequent clinical manifestations are largely dependent on the fungal burden at the time of exposure and the patient's underlying immune status. While the vast majority (>90%) of exposed individuals will remain asymptomatic, individuals seeking medical attention can present with a diverse set of symptoms ranging from a self-limited pulmonary illness to severe, disseminated disease. Individuals at risk for severe infection include those with impaired cellular immunity, patients who have undergone organ transplantation, are HIV positive, or have a hematologic malignancy. The available laboratory methods for the diagnosis of H capsulatum infection include fungal culture, molecular techniques, serologic testing, and antigen detection. While culture remains the gold standard diagnostic test and is highly specific, prolonged incubation is often required and sensitivity decreases (9%-34%) in cases of acute or localized disease. Similarly, molecular methods offer high specificity, but decreased sensitivity. Serologic testing likewise offers high specificity; however, results may be falsely negative in immunosuppressed patients or those who present with acute disease. Also, antibodies may persist for years following disease resolution, thereby limiting the clinical specificity. Detection of H capsulatum antigen from urine samples has improved...
sensitivity (80%-95%) for the diagnosis of active histoplasmosis compared to both culture and serology. Additionally, urine antigen levels can be followed to monitor patient response to therapy, with declining levels consistent with disease resolution. Notably, however, H capsulatum antigen may persist at low levels following completion of antifungal therapy and clinical improvement.

**Useful For:** Aids in the diagnosis of Histoplasma capsulatum infection Monitoring Histoplasma antigen titers in urine

**Interpretation:** Presence of Histoplasma antigen in urine is indicative of current or recent infection with H capsulatum. Declining levels of Histoplasma antigen are indicative of disease regression and can be used to monitor patient response to antifungal therapy. Notably, low-level titers may persist for extended periods of time following appropriate treatment and resolution of infection. Urine samples with "Indeterminate" results are automatically reflexed to MiraVista Diagnostics (Indianapolis, IN) for confirmatory testing. Clinical decisions regarding Histoplasma infection should not be based on an indeterminate result alone. Other laboratory findings, including Histoplasma serology, fungal culture, and molecular tests (eg, RT-PCR) should be considered, alongside clinical presentation and exposure history, to confirm the diagnosis. The absence of detectable Histoplasma antigen in urine is consistent with the absence of infection. Repeat testing on a fresh urine sample if early acute Histoplasma infection is suspected.

**Reference Values:**

**HISTOPLASMA ANTIGEN RESULT**

Negative

**HISTOPLASMA ANTIGEN VALUE**

Negative: 0.00-0.10
Indeterminate: 0.11-0.49
Positive: > or =0.50

**Clinical References:**


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**Histoplasma capsulatum/Blastomyces species Molecular Detection, PCR, Blood**

**Clinical Information:** Infections with Blastomyces dermatitidis and Histoplasma capsulatum cause a variety of clinical manifestations ranging from self-limited, mild pulmonary illness to potentially life-threatening, disseminated disease. Patients at risk for disseminated disease include neonates and immunosuppressed individuals, particularly those with AIDS, hematologic malignancies, or a recent transplant. Primary infections are acquired through inhalation of microconidia that are present in the environment. In the United States, most cases of blastomycosis and histoplasmosis occur along the Ohio and Mississippi River valleys. The gold standard for diagnosis of blastomycosis and histoplasmosis remains isolation of the organisms in culture. Although sensitive, recovery in culture and subsequent identification may require days to weeks. The organisms can be identified after growth in culture using traditional macro- and microscopic morphologic techniques or through the use of nucleic acid hybridization probes. Hybridization probe-based procedures are rapid and demonstrate good sensitivity and specificity from culture, although some cross-reactivity with relatively uncommon fungal organisms has been reported. Additional diagnostic tests that can be utilized for these organisms include stains, histopathology, serology, and antigen detection with each of these methods offering advantages and limitations depending on the stage of the illness and the status of the patient. Fungal stains (eg, calcofluor white) offer a rapid diagnostic approach, but demonstrate poor sensitivity and specificity. Serologic tests such as complement fixation and immunodiffusion are noninvasive, but are laborious, subjective, and may show low sensitivity, especially in immunocompromised hosts. Antigen detection also offers a noninvasive approach, but has been demonstrated to show cross-reactivity with antigens from closely
related fungal species. Molecular techniques have been established as sensitive and specific methods for the diagnosis of infectious diseases and have the added advantage of a rapid turnaround time for results. Due to the limitations of conventional diagnostic methods for blastomycosis and histoplasmosis, a single tube, real-time PCR assay was developed and verified for the detection and differentiation of B dermatitidis/gilchristii and H capsulatum directly from clinical specimens.

**Useful For:** Rapid detection of Histoplasma capsulatum and Blastomyces dermatitidis DNA in blood specimens

**Interpretation:** A positive result for Histoplasma capsulatum indicates presence of Histoplasma DNA; a positive result for Blastomyces dermatitidis indicates presence of Blastomyces DNA. A negative result indicates absence of detectable H capsulatum and B dermatitidis/gilchristii DNA.

**Reference Values:**
Not applicable

**Clinical References:**
PCR is negative.

Reference Values:
Not applicable


Histoplasma/Blastomyces Panel, Spinal Fluid
Clinical Information: Histoplasma Histoplasma capsulatum is a soil saprophyte that grows well in soil enriched with bird droppings. The usual disease is self-limited, affects the lungs, and is asymptomatic. Chronic cavitary pulmonary disease, disseminated disease, and meningitis may occur and can be fatal, especially in young children and immunosuppressed patients. Blastomyces The dimorphic fungus, Blastomyces dermatitidis, causes blastomycosis. When the organism is inhaled, it causes pulmonary disease: cough, pain, and hemoptysis, along with fever and night sweats. It commonly spreads to the skin, bone, or internal genitalia where suppuration and granulomas are typical. Occasionally, primary cutaneous lesions after trauma are encountered; however, this type of infection is uncommon. Central nervous system disease is uncommon.

Useful For: Histoplasma: Aiding in the diagnosis of Histoplasma meningitis Blastomyces: Detecting antibodies in patients having blastomycosis

Interpretation: Histoplasma: -Any positive serologic result in spinal fluid is significant. -Simultaneous appearance of the H and M precipitin bands indicates active histoplasmosis. -The M band alone indicates active or chronic disease or a recent skin test for histoplasmosis. Blastomyces: A positive result is suggestive of infection, but the results cannot distinguish between active disease and prior exposure. Furthermore, detection of antibodies in cerebrospinal fluid (CSF) may reflect intrathecal antibody production, or may occur due to passive transfer or introduction of antibodies from the blood during lumbar puncture. Routine fungal culture of clinical specimens (eg, CSF) is recommended in cases of suspected blastomycosis involving the central nervous system.

Reference Values:
Histoplasma ANTIBODY
Mycelial by complement fixation: Negative
Yeast by complement fixation: Negative
Antibody by immunodiffusion: Negative

Blastomyces ANTIBODY IMMUNODIFFUSION
Negative


HIV Antigen and Antibody Prenatal Routine Screen, Plasma
Clinical Information: AIDS is caused by 2 known types of HIV. HIV type 1 (HIV-1) is found in patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high risk for AIDS. The virus is transmitted by sexual contact, by exposure to infected blood or blood products, or from an infected mother to her fetus or infant. HIV type 2 (HIV-2) infection is endemic only in West Africa, and has been identified in individuals who had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in viral morphology, overall genomic structure, and its ability to cause AIDS.
Antibodies against HIV-1 and HIV-2 are usually not detectable until 6 to 12 weeks following exposure and are almost always detectable by 12 months. They may fall to undetectable levels (ie, seroreversion) in the terminal stage of AIDS when the patient's immune system is severely depressed. Routine serologic screening of patients at risk for HIV-1 or HIV-2 infection usually begins with a HIV-1/-2 antigen and/or antibody screening test, which may be performed by various FDA-approved assay methods, including rapid HIV antibody tests, enzyme immunoassays, and chemiluminescent immunoassays. In testing algorithms that begin with these methods, supplemental or confirmatory testing should be requested only for specimens that are repeatedly reactive by these methods according to assay manufacturers' instructions for use.

**Useful For:** Screening for HIV-1 and/or HIV-2 infection in nonsymptomatic pregnant patients

**Interpretation:** Negative HIV-1/-2 antigen and antibody screening test results usually indicate absence of HIV-1 and HIV-2 infection. However, such negative results do not rule-out acute HIV infection. If acute HIV-1 infection is suspected, detection of HIV-1 RNA (HIVQN / HIV-1 RNA Detection and Quantification, Plasma) or HIV-1 DNA and RNA (HIVP / HIV-1 DNA and RNA Qualitative Detection by PCR, Plasma) is recommended. Reactive HIV-1/-2 antigen and antibody screening test results suggest the presence of HIV-1 and/or HIV-2 infection, but it is not diagnostic for HIV infection and should be considered preliminary. A reactive result of this assay does not differentiate among reactivity with HIV-1 p24 antigen, HIV-1 antibody, and HIV-2 antibody. Diagnosis of HIV infection must be based on results of supplemental tests, such as HIV antibody confirmation/differentiation test (automatically reflexed on all samples with reactive screen test results at an additional charge). All initially positive supplemental or confirmatory HIV test results (by serologic or molecular test methods) should be verified by submitting a second serum specimen for repeat testing. Such positive HIV test results are required under laws in many states in the United States to be reported to the departments of health of the respective states where the patients reside. The following algorithms are available in Special Instructions: -HIV Testing Algorithm (Fourth Generation Screening Assay), Including Neonatal Testing and Follow-up of Reactive Rapid Serologic Test Results -HIV Prenatal Testing Algorithm, Including Follow-up of Reactive Rapid Serologic Test Results

**Reference Values:**

Negative

**Clinical References:**
**Useful For:** Diagnosis of HIV-1 and/or HIV-2 infection in cadaveric or hemolyzed serum specimens from symptomatic patients with or without risk factors for HIV infection

**Interpretation:** A reactive HIV-1/-2 antibody screen result obtained by EIA suggests the presence of HIV-1 and/or HIV-2 infection. However, it does not differentiate between HIV-1 and HIV-2 antibody reactivity. Diagnosis of HIV infection must be based on results of supplemental tests, such as HIV antibody confirmation/differentiation test (automatically reflexed on all samples with reactive screen test results at an additional charge). All presumptive antibody-positive test results should be verified by submitting a second serum specimen for retesting. A negative HIV-1/-2 antibody EIA screen result usually indicates the absence of HIV-1 or HIV-2 infection. However, for specimens that are reactive by the rapid HIV antibody tests, confirmatory testing is recommended even if the EIA results are negative.

**Reference Values:**
Negative

**Clinical References:**
1. Constantine N: HIV antibody assays May 2006. In HIV InSite Knowledge Base (online textbook). Available at http://hivinsite.ucsf.edu/InSite?page=kb-00&doc=kb-02-02-01

**HIV-1 and HIV-2 Antibody Confirmation and Differentiation Prenatal, Plasma**

**Clinical Information:** AIDS is caused by 2 known types of HIV. HIV type 1 (HIV-1) is found in patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high risk for AIDS. The virus is transmitted by sexual contact, by exposure to infected blood or blood products, or from an infected mother to her fetus or infant. HIV type 2 (HIV-2) infection is endemic only in West Africa, and it has been identified in individuals who had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in viral morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detectable until 6 to 12 weeks following exposure and are almost always detectable by 12 months. They may fall to undetectable levels (ie, seroreversion) in the terminal stage of AIDS when the patient's immune system is severely depressed. Routine serologic screening of patients at risk for HIV-1 or HIV-2 infection usually begins with a HIV-1/-2 antigen and/or antibody screening test, which may be performed by various FDA-approved assay methods, including rapid HIV antibody tests, enzyme immunoassays, and chemiluminescent immunoassays. In testing algorithms that begin with these methods, supplemental or confirmatory testing should be requested only for specimens that are repeatedly reactive by these methods according to assay manufacturers' instructions for use.

**Useful For:** Confirmation and differentiation of HIV-1 and HIV-2 antibodies in plasma specimens from prenatal patients who show reactive results with third- (HIV-1/-2 antibody only) and fourth-generation (HIV antigen and antibody) HIV serologic assays

**Interpretation:** Negative results for both HIV-1 and HIV-2 antibodies usually indicate the absence of HIV-1 and HIV-2 infection. However, in patients with reactive initial combined HIV-1/-2 antigen and antibody test results, such negative results do not rule-out acute or early HIV infection. In this situation, the HIV-1 RNA reflex test will be performed. Positive HIV-1 antibody but negative HIV-2 antibody results indicates the presence of HIV-1 infection. Together with reactive initial combined HIV-1/-2 antigen and antibody test results, individuals with such results are presumed to have HIV-1 infection. Verification of a first-time positive test result is recommended for the diagnosis of HIV-1 infection. Additional testing with a newly submitted plasma specimen for HIQNP / HIV-1 RNA Detection and Quantification Prenatal, Plasma is recommended to verify and confirm the diagnosis of HIV-1 infection prior to initiating antiretroviral treatment. Positive HIV-1 antibody but indeterminate HIV-2 antibody results indicates the presence of HIV-1 infection, with probable cross-reactivity of HIV-1 antibodies with
HIV-2 antigens on the assay strip. Verification of a first-time positive test result is recommended for the diagnosis of HIV-1 infection. Submit a plasma specimen for detection of HIV-1 RNA (HIQNP / HIV-1 RNA Detection and Quantification Prenatal, Plasma. However, such result patterns may rarely indicate early HIV-2 infection (ie, HIV-2 coinfection) in HIV-1-infected individuals. For individuals at risk for HIV-2 infection (based on epidemiologic exposure history), a plasma specimen should be submitted also for FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR. Indeterminate HIV-1 antibody but negative HIV-2 antibody results suggest either very early HIV-1 infection (in individuals with risk factors) or the presence of nonspecific cross-reactivity between the patients' specimens and HIV-1 antigens on the assay strip. In this situation, the HIV-1 RNA reflex test will be performed. Negative HIV-1 antibody, but indeterminate HIV-2 antibody results, may be due to acute HIV-1 infection or suggests either very early HIV-2 infection (in individuals with risk factors) or presence of nonspecific cross-reactivity between the patients' specimens and HIV-2 antigens on the assay strip. In this situation, the HIV-1 RNA reflex test will be performed. If the subsequent HIV-1 RNA test result is negative and patient has known risk factors for HIV-2 infection (based on patient's clinical and epidemiologic history), a new specimen should be submitted for HIV-2 serologic testing (HIV2L/ HIV-2 Antibody Confirmation, Serum) or FHV2Q / HIV-2 DNA/RNA detection (FHV2Q). Positive results for both HIV-1 and HIV-2 antibodies suggest probable the presence of HIV-1 and HIV-2 coinfection. However, such results may be rarely due to: a) HIV-1 infection with HIV-2 antibody cross-reactivity; or b) HIV-2 infection with HIV-1 antibody cross-reactivity (eg, absence of HIV-1 p24 and p31 bands). Verification of a first-time positive test result is recommended for the diagnosis of HIV infection. Based on patient's clinical and epidemiologic history, plasma specimens should be submitted for detection of HIQNP / HIV-1 RNA Detection and Quantification Prenatal, Plasma or FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR Indeterminate results for both HIV-1 and HIV-2 antibodies indicate either very early HIV infection (in individuals with risk factors) or the presence of nonspecific cross-reactivity between the patients' specimens and HIV antigens on the assay strip. Nonspecific cross-reactivity may be due to recent non-HIV infections, hypergammaglobulinemic states, connective tissue disorders, or pregnancy (alloantibodies). If acute or early HIV infection is suspected, the HIV-1 RNA reflex test will be performed. Negative HIV-1 antibody but positive HIV-2 antibody results indicates the presence of HIV-2 infection. Together with a reactive initial HIV-1/-2 antigen and antibody screening test results, individuals with such results are presumed to have HIV-2 infection. Additional testing with a newly submitted plasma specimen for FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR is recommended to verify and confirm the diagnosis of HIV-2 infection prior to initiating antiretroviral treatment. Reactive HIV-1 antibody but positive HIV-2 antibody results usually indicate the presence of HIV-2 infection with HIV-1 antibody cross-reactivity (eg, presence of only HIV-1 gp41 and/or gp160 band). However, such results may be rarely due to HIV-1 and HIV-2 coinfection. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection, by submitting a new specimen for HIV-2 serologic testing or a plasma specimen for FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR. If the patient is at risk for HIV-1 infection (based on patient's clinical and epidemiologic history), a plasma specimen should be submitted also for detection of HIQNP / HIV-1 RNA Detection and Quantification Prenatal, Plasma. Indeterminate HIV-1 antibody but positive HIV-2 antibody results indicate the presence of HIV-2 infection, with probable cross-reactivity of HIV-2 antibodies with HIV-1 antigens on the assay strip. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection, by submitting a plasma specimen for FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR. However, such result patterns may rarely indicate early HIV-1 infection (ie, HIV-1 coinfection) in HIV-2-infected individuals. For individuals at risk for HIV-1 infection, (based on epidemiologic exposure history), plasma specimen should be submitted also for detection of HIQNP / HIV-1 RNA Detection and Quantification Prenatal, Plasma. The following algorithms are available in Special Instructions: -HIV Testing Algorithm (Fourth-Generation Screening Assay), Including Neonatal Testing and Follow-up of Reactive Rapid Serologic Test Results -HIV Prenatal Testing Algorithm, Including Follow-up of Reactive Rapid Serologic Test Results

Reference Values:
Negative

HIV-1 and HIV-2 Antibody Confirmation and Differentiation, Plasma

Clinical Information: AIDS is caused by 2 known types of HIV. HIV type 1 (HIV-1) is found in patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high risk for AIDS. The virus is transmitted by sexual contact, by exposure to infected blood or blood products, or from an infected mother to her fetus or infant. HIV type 2 (HIV-2) infection is endemic only in West Africa, and it has been identified in individuals who had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in viral morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detectable until 6 to 12 weeks following exposure and are almost always detectable by 12 months. They may fall to undetectable levels (ie, seroreversion) in the terminal stage of AIDS when the patient's immune system is severely depressed. Routine serologic screening of patients at risk for HIV-1 or HIV-2 infection usually begins with a HIV-1/-2 antigen and/or antibody screening test, which may be performed by various FDA-approved assay methods, including rapid HIV antibody tests, enzyme immunoassays, and chemiluminescent immunoassays. In testing algorithms that begin with these methods, supplemental or confirmatory testing should be requested only for specimens that are repeatedly reactive by these methods according to assay manufacturers' instructions for use.

Useful For: Confirmation and differentiation of HIV-1 and HIV-2 antibodies in plasma specimens that show reactive results with third-(HIV-1/-2 antibody only) and fourth-generation (HIV antigen and antibody) HIV serologic assays

Interpretation: Negative results for both HIV-1 and HIV-2 antibodies usually indicate the absence of HIV-1 and HIV-2 infection. However, in patients with reactive initial combined HIV-1/-2 antigen and antibody test results, such negative results do not rule-out acute or early HIV infection. If acute or early HIV infection is suspected, The HIV-1 RNA reflex test will be performed. Positive HIV-1 antibody, but negative HIV-2 antibody results, indicates the presence of HIV-1 infection. Together with reactive initial combined HIV-1/-2 antigen and antibody test results, individuals with such results are presumed to have HIV-1 infection. Verification of a first-time positive test result is recommended for the diagnosis of HIV-1 infection. Additional testing with a newly submitted plasma specimen for HIVQN / HIV-1 RNA Detection and Quantification, Plasma is recommended to verify and confirm the diagnosis of HIV-1 infection prior to initiating antiretroviral treatment. Positive HIV-1 antibody but indeterminate HIV-2 antibody results indicate the presence of HIV-1 infection, with probable cross-reactivity of HIV-1 antibodies with HIV-2 antigens on the assay strip. Verification of a first-time positive test result is recommended for the diagnosis of HIV-1 infection. Submit a plasma specimen for detection of HIVQN / HIV-1 RNA Detection and Quantification, Plasma. However, such result patterns may rarely indicate early HIV-2 infection (ie, HIV-2 coinfection) in HIV-1-infected individuals. For individuals at risk for HIV-2 infection (based on epidemiologic exposure history), a plasma specimen should be submitted also for FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR. Indeterminate HIV-1 antibody but negative HIV-2 antibody results suggest either very early HIV-1 infection (in individuals with risk factors) or the presence of nonspecific cross-reactivity between the patients' specimens and HIV-1 antigens on the assay strip. In this situation, the HIV-1 RNA reflex test will be performed. Negative HIV-1 antibody, but indeterminate HIV-2 antibody results, may be due to acute HIV-1 infection or suggests either very early HIV-2 infection (in individuals with risk factors) or presence of nonspecific cross-reactivity between the patients' specimens and HIV-2 antigens on the assay strip. In this situation, the HIV-1 reflex test will be performed. If the subsequent HIV-1 RNA test result is negative and patient has known risk factors for HIV-2 infection (based on patient's clinical and epidemiologic history), a new specimen should be submitted for HIV-2 serologic testing (HIV2L / HIV-2 Antibody Confirmation, Serum) or FHV2Q /
HIV-2 DNA/RNA detection. Positive results for both HIV-1 and HIV-2 antibodies suggest probable the presence of HIV-1 and HIV-2 coinfection. However, such results may be rarely due to: a) HIV-1 infection with HIV-2 antibody cross-reactivity; or b) HIV-2 infection with HIV-1 antibody cross-reactivity (e.g., absence of HIV-1 p24 and p31 bands). Verification of a first-time positive test result is recommended for the diagnosis of HIV infection. Based on patient's clinical and epidemiologic history, plasma specimens should be submitted for detection of HIV-1 RNA (HIVQN / HIV-1 RNA Detection and Quantification, Plasma) or HIV-2 DNA/RNA (FHV2A / HIV-2 DNA/RNA Qualitative Real-Time PCR). Indeterminate results for both HIV-1 and HIV-2 antibodies indicate either very early HIV infection (in individuals with risk factors) or the presence of nonspecific cross-reactivity between the patients' specimens and HIV antigens on the assay strip. Nonspecific cross-reactivity may be due to recent non-HIV infections, hypergammaglobulinemic states, connective tissue disorders, or pregnancy (alloantibodies). If acute or early HIV infection is suspected, the HIV-1 RNA reflex test will be performed. Negative HIV-1 antibody but positive HIV-2 antibody results indicates the presence of HIV-2 infection. Together with a reactive initial HIV-1/-2 antigen and antibody screening test results, individuals with such results are presumed to have HIV-2 infection. Additional testing with a newly submitted plasma specimen for FHV2QA / HIV-2 DNA/RNA Qualitative Real-Time PCR is recommended to verify and confirm the diagnosis of HIV-2 infection prior to initiating antiretroviral treatment. Reactive HIV-1 antibody but positive HIV-2 antibody results usually indicate the presence of HIV-2 infection with HIV-1 antibody cross-reactivity (e.g., presence of only HIV-1 gp41 and/or gp160 band). However, such results may be rarely due to HIV-1 and HIV-2 coinfection. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection, by submitting a plasma specimen for FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR. If the patient is at risk for HIV-1 infection (based on patient's clinical and epidemiologic history), a plasma specimen should be submitted also for detection of HIV-1 RNA (HIVQN / HIV-1 RNA Detection and Quantification, Plasma). Indeterminate HIV-1 antibody but positive HIV-2 antibody results indicate the presence of HIV-2 infection, with probable cross-reactivity of HIV-2 antibodies with HIV-1 antigens on the assay strip. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection, by submitting a plasma specimen for FHV2QA / HIV-2 DNA/RNA Qualitative Real-Time PCR. However, such result patterns may rarely indicate early HIV-1 infection (i.e., HIV-1 coinfection) in HIV-2-infected individuals. For individuals at risk for HIV-1 infection, (based on epidemiologic exposure history), plasma specimen should be submitted also for detection of HIVQN / HIV-1 RNA Detection and Quantification, Plasma. See HIV Testing Algorithm (Fourth-Generation Screening Assay), Including Neonatal Testing and Follow-up of Reactive Rapid Serologic Test Results in Special Instructions.

Reference Values:
Negative

Clinical References:
ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detectable until 6 to 12 weeks following exposure and are almost always detectable by 12 months. They may fall to undetectable levels (ie, seroreversion) in the terminal stage of AIDS when the patient's immune system is severely depressed. Routine serologic screening of patients at risk for HIV-1 or HIV-2 infection usually begins with a HIV-1/-2 antigen and/or antibody screening test, which may be performed by various FDA-approved assay methods, including rapid HIV antibody tests, enzyme immunoassays, chemiluminescent immunoassays. In testing algorithms that begin with these methods, supplemental or confirmatory testing should be requested only for specimens that are repeatedly reactive by these methods according to assay manufacturers' instructions for use.

**Useful For:** Confirmation and differentiation of HIV-1 and HIV-2 antibodies in serum specimens that show reactive results with third- (HIV-1/-2 antibody only) and fourth- (HIV antigen and antibody) generation HIV serologic assays

**Interpretation:** Negative results for both HIV-1 and HIV-2 antibodies usually indicate the absence of HIV-1 and HIV-2 infection. However, in patients with reactive initial combined HIV-1/-2 antigen and antibody test results, such negative results do not rule-out acute or early HIV infection. If acute or early HIV infection is suspected, detection of HIV-1 RNA (HIVDQ / HIV-1 RNA Detection and Quantification, Plasma) and/or HIV-2 DNA/RNA (FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR) is recommended, based on patient's clinical and epidemiologic exposure history. Positive HIV-1 antibody, but negative HIV-2 antibody results, indicates the presence of HIV-1 infection. Together with reactive initial combined HIV-1/-2 antigen and antibody test results, individuals with such results are presumed to have HIV-1 infection. Verification of a first-time positive test result is recommended for the diagnosis of HIV-1 infection. Additional testing with a newly submitted plasma specimen for HIV-1 RNA (HIVDQ) is recommended to verify and confirm the diagnosis of HIV-1 infection prior to initiating antiretroviral treatment. Positive HIV-1 antibody, but indeterminate HIV-2 antibody results, indicates the presence of HIV-1 infection. Submit a plasma specimen for detection of HIV-1 RNA (HIVDQ). However, such result patterns may rarely indicate early HIV-2 infection (ie, HIV-2 coinfection) in HIV-1-infected individuals. For individuals at risk for HIV-2 infection (based on epidemiologic exposure history), a plasma specimen should be submitted also for HIV-2 DNA/RNA (FHV2Q). Indeterminate HIV-1 antibody, but negative HIV-2 antibody results, suggest either very early HIV-1 infection (in individuals with risk factors) or the presence of nonspecific cross-reactivity between the patients' specimens and HIV-1 antigens on the assay strip. If patient has known risk factors for HIV-1 infection, a new specimen should be submitted for HIV-2 serologic testing (HIV2 / HIV-2 Antibody Evaluation, Serum or HIV2M / HIV-2 Antibody Screen, Serum) or HIV-2 DNA/RNA (FHV2Q). Negative HIV-1 antibody, but indeterminate HIV-2 antibody results, suggests either very early HIV-2 infection (in individuals with risk factors) or presence of nonspecific cross-reactivity between the patients' specimens and HIV-2 antigens on the assay strip. If patient has known risk factors for HIV-2 infection (based on patient's clinical and epidemiologic history), a new specimen should be submitted for HIV-2 serologic testing (HIV2 or HIV2M) or HIV-2 DNA/RNA (FHV2Q). Positive results for both HIV-1 and HIV-2 antibodies suggest probable the presence of HIV-1 and HIV-2 coinfection. However, such results may be rarely due to: a) HIV-1 infection with HIV-2 antibody cross-reactivity; or b) HIV-2 infection with HIV-1 antibody cross-reactivity (eg, absence of HIV-1 p24 and p31 bands). Verification of a first-time positive test result is recommended for the diagnosis of HIV infection. Based on patient's clinical and epidemiologic history, plasma specimens should be submitted for detection of HIV-1 RNA (HIVDQ) and/or HIV-2 DNA/RNA (FHV2Q).

Indeterminate results for both HIV-1 and HIV-2 antibodies indicate either very early HIV infection (in individuals with risk factors) or the presence of nonspecific cross-reactivity between the patients' specimens and HIV antigens on the assay strip. Nonspecific cross-reactivity may be due to recent non-HIV infections, hypergammaglobulinemic states, connective tissue disorders, or pregnancy (alloantibodies). For individuals at risk for HIV infection, plasma specimens should be submitted for detection of HIV-1 RNA (HIVDQ) and/or HIV-2 DNA/RNA (FHV2Q), depending on the epidemiologic exposure history. Negative HIV-1 antibody, but positive HIV-2 antibody results, indicates the presence of HIV-2 infection. Together with a reactive initial HIV-1/-2 antigen and antibody screening test results, individuals with such results are presumed to have HIV-2 infection. Additional testing with a newly submitted plasma specimen for HIV-2 DNA/RNA (FHV2Q) is recommended to verify and confirm the diagnosis of HIV-2 infection prior to initiating antiretroviral treatment. Reactive HIV-1 antibody, but
positive HIV-2 antibody results, usually indicates the presence of HIV-2 infection with HIV-1 antibody cross-reactivity (eg, presence of only HIV-1 gp41 and/or gp160 band). However, such results may be rarely due to HIV-1 and HIV-2 coinfection. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection, by submitting a new specimen for HIV-2 serologic testing (HIV2 or HIV2M) or a plasma specimen for HIV-2 DNA/RNA (FHV2Q). If the patient is at risk for HIV-1 infection (based on patient's clinical and epidemiologic history), a plasma specimen should be submitted also for detection of HIV-1 RNA (HIVDQ). Indeterminate HIV-1 antibody, but positive HIV-2 antibody results, indicates the presence of HIV-2 infection, with probable cross-reactivity of HIV-2 antibodies with HIV-1 antigens on the assay strip. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection, by submitting a plasma specimen for (FHV2Q). However, such result patterns may rarely indicate early HIV-1 infection (ie, HIV-1 coinfection) in HIV-2-infected individuals. For individuals at risk for HIV-1 infection, (based on epidemiologic exposure history), plasma specimen should be submitted also for detection of HIV-1 RNA (HIVDQ). See HIV Testing Algorithm (Fourth-Generation Screening Assay), Including Neonatal Testing and Follow-up of Reactive Rapid Serologic Test Results in Special Instructions.

**Reference Values:**

Negative

**Clinical References:**


**HIV-1 and HIV-2 Antibody Screen for Hemolyzed Specimens, Serum**

**Clinical Information:** Epidemiological data indicate that AIDS is caused by at least 2 types of HIV. The first virus, HIV-1, has been isolated from patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high risk for AIDS. HIV-1 is transmitted by sexual contact, exposure to infected blood or blood products, or from an infected mother to her fetus or infant. A second HIV virus, HIV-2, was isolated from patients in West Africa in 1986. HIV-2 appears to be endemic only in West Africa, but it also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detected until 6 to 12 weeks following exposure and are almost always detected by 12 months. They may fall into undetectable levels in the terminal stage of AIDS. See HIV Testing Algorithm (Fourth-Generation Screening Assay), Including Neonatal Testing and Follow-up of Reactive Rapid Serologic Test Results in Special Instructions.

**Useful For:** Screening cadaveric or hemolyzed serum specimens for HIV-1 and/or HIV-2 infection in non-symptomatic patients with or without risk factors for HIV infection. This assay kit is FDA-approved for testing cadaveric or hemolyzed blood specimens.

**Interpretation:** A reactive HIV-1/2 antibody screen result obtained by EIA suggests the presence of HIV-1 and/or HIV-2 infection. However, it does not differentiate between HIV-1 and HIV-2 antibody reactivity. Diagnosis of HIV infection must be based on results of supplemental tests, such as HIV antibody confirmation/differentiation test (automatically reflexed on all samples with reactive screen test results at an additional charge). All presumptive antibody-positive test results should be verified by submitting a second serum specimen for retesting. A negative HIV-1/2 antibody EIA screen result
usually indicates the absence of HIV-1 or HIV-2 infection. However, for specimens that are reactive by the rapid HIV antibody tests, confirmatory testing is recommended even if the EIA results are negative.

**Reference Values:**
Negative

**Clinical References:**
1. Constantine N: HIV antibody assays May 2006. In HIV InSite Knowledge Base (online textbook). Available at: http://hivinsite.ucsf.edu/InSite?page=kb-00&doc=kb-02-02-01

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**HIV-1 and HIV-2 Antigen and Antibody Diagnostic Evaluation, Plasma**

**Clinical Information:** AIDS is caused by 2 known types of HIV. HIV type 1 (HIV-1) is found in patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high risk for AIDS. The virus is transmitted by sexual contact, by exposure to infected blood or blood products, or from an infected mother to her fetus or infant. HIV type 2 (HIV-2) infection is endemic only in West Africa, and it has been identified in individuals who had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in viral morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detectable until 6 to 12 weeks following exposure and are almost always detectable by 12 months. They may fall to undetectable levels (ie, seroreversion) in the terminal stage of AIDS when the patient’s immune system is severely depressed. Routine serologic screening of patients at risk for HIV-1 or HIV-2 infection usually begins with a HIV-1/-2 antigen and/or antibody screening test, which may be performed by various FDA-approved assay methods, including rapid HIV antibody tests, enzyme immunoassays, and chemiluminescent immunoassays. In testing algorithms that begin with these methods, supplemental or confirmatory testing should be requested only for specimens that are repeatedly reactive by these methods according to assay manufacturers' instructions for use.

**Useful For:** Diagnosing HIV-1 and/or HIV-2 infection in symptomatic patients more than 2 years old
Follow-up testing of individuals with reactive rapid HIV test results

**Interpretation:** Negative HIV-1/-2 antigen and antibody screening test results usually indicate the absence of HIV-1 and HIV-2 infection. However, such negative results do not rule-out acute HIV infection. If acute HIV-1 infection is suspected, it is recommended that a specimen be submitted for detection of HIV-1 RNA (HIVQN / HIV-1 RNA Detection and Quantification, Plasma) or HIV-1 DNA and RNA (HIVP / HIV-1 DNA and RNA Qualitative Detection by PCR, Plasma). Reactive HIV-1/-2 antigen and antibody screening test results suggest the presence of HIV-1 and/or HIV-2 infection, but it is not diagnostic for HIV infection and should be considered preliminary. Reactive result of this assay does not differentiate among reactivity with HIV-1 p24 antigen, HIV-1 antibody, and HIV-2 antibody.

Diagnosis of HIV infection must be based on results of supplemental tests, such as HIV antibody confirmation/differentiation test (automatically reflexed on all samples with reactive screen test results at an additional charge). All initially positive supplemental or confirmatory HIV test results (by serologic or molecular test methods) should be verified by submitting a second serum specimen for repeat testing. Such positive HIV test results are required under laws in many states in the United States to be reported to the departments of health of the respective states where the patients reside. The following algorithms are available in Special Instructions: -HIV Testing Algorithm (Fourth Generation Screening Assay), Including Neonatal Testing and Follow-up of Reactive Rapid Serologic Test Results -HIV Prenatal Testing Algorithm, Including Follow-up of Reactive Rapid Serologic Test Results

**Reference Values:**
Negative
**Clinical Information:** AIDS is caused by 2 known types of HIV. HIV type 1 (HIV-1) is found in patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high risk for AIDS. The virus is transmitted by sexual contact, by exposure to infected blood or blood products, or from an infected mother to her fetus or infant. HIV type 2 (HIV-2) infection is endemic only in West Africa, and it has been identified in individuals who had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in viral morphology, overall genomic structure, and its ability to cause AIDS. Antibodies against HIV-1 and HIV-2 are usually not detectable until 6 to 12 weeks following exposure and are almost always detectable by 12 months. They may fall to undetectable levels (ie, seroreversion) in the terminal stage of AIDS when the patient’s immune system is severely depressed. Routine serologic screening of patients at risk for HIV-1 or HIV-2 infection usually begins with a HIV-1/-2 antigen and/or antibody screening test, which may be performed by various FDA-approved assay methods, including rapid HIV antibody tests, enzyme immunoassays, and chemiluminescent immunoassays. In testing algorithms that begin with these methods, supplemental or confirmatory testing should be requested only for specimens that are repeatedly reactive by these methods according to assay manufacturers' instructions for use.

**Useful For:** Screening for HIV-1 and HIV-2 infection in nonsymptomatic, nonpregnant individuals older than 2 years

**Interpretation:** Negative HIV-1/-2 antigen and antibody screening test results usually indicate absence of HIV-1 and HIV-2 infection. However, such negative results do not rule-out acute HIV infection. If acute HIV-1 infection is suspected, detection of HIV-1 RNA (HIVQN / HIV-1 RNA Quantification and Detection, Plasma) or HIV-1 DNA and RNA (HIVP / HIV-1 DNA and RNA Qualitative Detection by PCR, Plasma) is recommended. Reactive HIV-1/-2 antigen and antibody screening results suggest the presence of HIV-1 and/or HIV-2 infection, but it is not diagnostic for HIV infection and should be considered preliminary. A reactive result does not differentiate among reactivity with HIV-1 p24 antigen, HIV-1 antibody, and HIV-2 antibody. Diagnosis of HIV infection must be based on results of supplemental tests, such as the HIV antibody confirmation and differentiation reflex (automatically reflexed on all samples with reactive screen test results at an additional charge). All initially positive supplemental or confirmatory HIV test results (by serologic or molecular test methods) should be verified by submitting a second serum specimen for repeat testing. Such positive HIV test results are required under laws in many states in the United States to be reported to the departments of health of the respective states where the patients reside. See HIV Testing Algorithm (Fourth Generation Screening Assay), Including Neonatal Testing and Follow-up of Reactive Rapid Serologic Test Results in Special Instructions.

**Reference Values:**

Negative

HIV-1 DNA and RNA Qualitative Detection by PCR, Plasma

Clinical Information: Human immunodeficiency virus (HIV)-1 infection is usually confirmed by detection of HIV-1-specific antibodies in serum. However, serologic testing may not reliably identify HIV-1 infection in neonates with passively acquired maternal HIV-1 antibodies or with incompletely developed immune systems, individuals with early HIV-1 infection (<30 days from infection), or individuals with "indeterminate" HIV-1 antibody results by supplemental serologic assays. In these situations, detection of HIV-1 nucleic acids (RNA or proviral DNA) by PCR can provide definitive, early evidence of HIV-1 infection (approximately 10 to 14 days after infection), when results of routine diagnostic assays may be inconclusive. Upon entry into human cells (including peripheral blood mononuclear cells), the HIV-1 RNA is converted into complementary DNA (cDNA) by reverse transcription. These linear cDNA strands are then integrated into the host cell genome, thus representing the proviral form of HIV-1. mRNA, transcribed from the proviral DNA, is used to synthesize the proteins required to make new viral particles. These proteins and viral RNA are packaged in the host's cytoplasm and released from the cell, completing the life cycle of the virus. For infants born to HIV-1-infected mothers, HIV-1 DNA or RNA tests are recommended at 0 to 2 days, 14 days, 1 to 2 months, and 4 to 6 months after birth. Two consecutive positive HIV-1 virologic test results (HIV-1 DNA and/or RNA) are necessary for confirming the diagnosis of HIV-1 infection in infants younger than 18 months of age.

Useful For: Virologic detection of HIV-1 infection in infants younger than 18 months of age (an age group for which serologic tests are unreliable) born to HIV-1-infected mothers Early detection of acute HIV-1 infection in children and adults who may be receiving combination antiretroviral prophylaxis or preemptive treatment Determining eradication of HIV-1 in individuals receiving combination highly active antiretroviral therapies

Interpretation: A "Detected" result is consistent with HIV infection (see Cautions section). Per CDC and US Public Health Services recommendations, a second specimen should be collected from any patient with first-time detectable HIV-1 DNA or RNA result and tested to verify the diagnosis of HIV-1 infection. An "Undetected" result indicates that neither HIV-1 DNA nor RNA is detected in the specimen (see Cautions). Repeat testing is recommended at 0 to 2 days, 14 days, 1 to 2 months, and 4 to 6 months after birth in infants born to HIV-1-infected mothers. For at-risk individuals older than 18 months of age, repeat testing in 1 to 2 months is recommended. The lower limits of detection (based on 95% detection rate) of this assay in plasma are 311 copies/mL for HIV-1 DNA and 75 copies/mL for HIV-1 RNA. An "Inconclusive" result indicates that the absence or presence of HIV-1 DNA or RNA could not be determined with certainty after repeat testing of the clinical specimens in the laboratory, possibly due to PCR inhibition. Submission of a new specimen for testing is recommended.

Reference Values:
Undetected

Clinical References:

HIV-1 Genotypic Integrase Inhibitor Drug Resistance, Plasma

Clinical Information: Antiviral resistance may compromise highly active antiretroviral therapy
(HAART) in HIV-1-infected patients receiving HAART. When combination therapy fails, detection and analysis of HIV genotypic mutations can guide necessary changes to antiretroviral therapy and decrease HIV-1 viral load, thereby improving patient outcome. HIV-1 is an RNA virus that infects cells and is then converted to complementary DNA (cDNA) by the action of the viral reverse transcriptase (RT). RT has little proofreading capacity and therefore incorporates errors in the proviral DNA. These errors are transcribed into infectious viral particles when the proviral DNA is transcribed into RNA. Similarly, the enzyme protease (PR) catalyzes a polyprotein to produce peptides necessary for active viral replication. Although HAART (combinations of nucleoside analogs, nonnucleoside agents, protease inhibitors and/or integrase strand transfer inhibitors) may be effective in reducing viral load, genotypic mutations arising in drug-targeted HIV loci due to selective pressure from antiviral therapy can result in antiviral resistance that may compromise such therapy. Amplification and analysis of drug-targeted HIV-1 sequences allows identification of changes in nucleotide sequence and associated amino acid codons that may cause antiviral drug resistance. Such genotypic changes are identified by comparing the sequence data of the patient's HIV-1 strain to that of a wild-type HIV-1 strain. The significance of these genotypic mutations in relation to antiviral resistance is then determined by a set of interpretive rules developed and used by the Stanford HIVdb Program Genotypic Resistance Interpretation Algorithm (http://sierra2.stanford.edu/sierra/servlet/JSierra) for final interpretation. In the Stanford HIVdb program, genotypic mutations are categorized and interpreted according to phenotypic antiviral susceptibility tests performed using the ViroLogic PhenoSense assay (Monogram Biosciences Inc, San Francisco, US) or a HeLa-CD4 reporter gene assay. Each mutation is assigned a drug penalty score and the total score generated from all of the mutations relevant to the specific antiviral drug is used to estimate the level of resistance to that drug. These interpretive rules may be updated periodically by the Stanford HIVdb Team after reviewing newly published data on HIV-1 genotypic drug resistance mutations.

**Useful For:** Identification of HIV-1 genotypic mutations in the integrase region of HIV-1 to predict antiretroviral drug resistance in HIV-1-infected patients receiving integrase strand transfer inhibitors (ie, dolutegravir, elvitegravir, raltegravir) Guiding initiation or change of drug combinations for the treatment of HIV-1 infection

**Interpretation:** Detectable HIV-1 genotypic mutations conferring resistance to an antiviral drug are reported as amino acid codon changes (eg, N155H), along with associated resistance interpretations for the current FDA-approved integrase strand transfer inhibitors (dolutegravir, elvitegravir, and raltegravir). Interpretation for resistance to bictegravir is not available at present. Susceptible (SUSC) indicates that the genotypic mutations present in patient’s HIV-1 strain have not been associated with resistance to the specific drug (Stanford HIVdb total score 0 to 9). Potential Low-Level Resistance (PLR) indicates that genotypic mutations detected have been associated with possible reduction in susceptibility to the specific drug (Stanford HIVdb score 10 to 14). Low-Level Resistance (LR) indicates that genotypic mutations detected have been associated with reduction in susceptibility to the specific drug (Stanford HIVdb score 15 to 29). Intermediate Resistance (IR) indicates that genotypic mutations detected have been associated with reduction in susceptibility to the specific drug (Stanford HIVdb score 30 to 59). High-level Resistance (HR) indicates that genotypic mutations detected have been associated with maximum reduction in susceptibility to the specific drug (Stanford HIVdb score > or =60). Unable to Genotype indicates that viral target sequences are of poor quality to reliably determine antiviral resistance. This result may be due to low viral load, ambiguous or incomplete viral target sequences, presence of PCR inhibitors, and/or mutations in the PCR or sequencing primer binding regions. Inconclusive indicates inability of the assay to reliably determine antiviral resistance because of the presence of PCR inhibitors, mutations in the PCR or sequencing primer binding regions, or ambiguous or incomplete viral target sequences that did not allow reliable analysis to determine antiviral resistance.

**Reference Values:**
Not applicable

HIV-1 Genotypic Protease and Reverse Transcriptase Inhibitor Drug Resistance, Plasma

Clinical Information: Antiviral resistance may compromise highly active antiretroviral therapy (HAART) in HIV-infected patients receiving HAART. When combination therapy fails, detection and analysis of HIV genotypic mutations can guide necessary changes to antiretroviral therapy and decrease HIV viral load, thereby improving patient outcome. HIV-1 is an RNA virus that infects cells and is then converted to complementary DNA (cDNA) by the action of the viral reverse transcriptase (RT) gene product. RT has little proofreading capacity and, therefore, incorporates errors in the proviral DNA. These errors are transcribed into infectious viral particles when the proviral DNA is transcribed into RNA. Similarly, the enzyme protease catalyzes a polyprotein to produce peptides necessary for active viral replication. Although HAART (combination of nucleoside analog, nonnucleoside agent and/or protease inhibitor) may be effective in reducing the viral load, genotypic mutations arising in the drug-targeted HIV gene loci due to selective pressure from antiviral therapy result in antiviral resistance that may compromise such therapy. Amplification and analysis of drug-targeted HIV-gene sequence allows identification of changes in nucleotide bases and associated amino acid codons that may cause antiviral drug resistance. Such genotypic changes are deemed as mutations by comparing the sequence data of the patient's HIV strain to those of a wild-type HIV strain. The significance of these genotypic mutations in relation to antiviral resistance is then determined by a set of interpretive rules developed by a consensus panel of leading experts in the field of HIV resistance. Relevant data presented at a recognized scientific conference or published in peer-reviewed journals are considered by the consensus panel in developing these rules. When necessary, reliable unpublished drug resistance data known to consensus panel members may be considered in the process. The interpretive rules are updated by the consensus panel annually after reviewing newly published data on HIV-1 genotypic drug resistance mutations.

Useful For: Identification of HIV-1 genotypic mutations associated with resistance to nucleotide reverse-transcriptase inhibitors, non-nucleotide reverse-transcriptase inhibitors, and protease inhibitors. Guiding initiation or change of drug combinations for the treatment of HIV-1 infection.

Interpretation: Detectable HIV-1 genotypic mutations conferring resistance to an antiviral drug are reported as amino acid codon changes (eg, M184V) resulting from the mutations. Susceptible (Susc) indicates that the genotypic mutations present in patient's HIV-1 strain have not been associated with resistance to the specific drug in question. Resistant (Resist) indicates that genotypic detected have been associated with maximum reduction in susceptibility to the specific drug. Possible Resistance (PR) indicates that genotypic mutations detected have been associated with 1 or both of the following outcomes: -Diminished virologic response in some, but not all, patients having virus with these mutations; -Intermediate decrease in susceptibility of the virus to the specific drug. Unable to genotype indicates that the sequence data obtained are of poor quality to determine the presence or absence of genotypic resistant mutations in the patient's HIV strain. Probable cause of such poor sequence data is polymorphism in the region of the sequencing primers interfering with primer binding and subsequent sequencing reaction. Inconclusive indicates inability of the assay to reliably determine antiviral resistance because of either low HIV-1 viral load (ie, <500 copies/mL) or ambiguous or incomplete viral target sequences generated from the assay.

Reference Values: Not applicable

https://www.iasusa.org/content/antiretroviral-drug-resistance-testing-adult-hiv-1-infection
2. Ceccherini-Silberstein F, Cento V, Calvez V, Perno C-F: The use of human immunodeficiency virus
HIV-1 RNA Detection and Quantification, Plasma

Clinical Information: Currently, 2 types of HIV, HIV type 1 (HIV-1) and HIV type 2 (HIV-2), are known to infect humans. HIV-1 has been isolated from patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high-risk for AIDS. Accounting for more than 99% of HIV infection in the world, HIV-1 is transmitted by sexual contact, by exposure to infected blood or blood products, from an infected pregnant woman to fetus in utero or during birth, or from an infected mother to infant via breast-feeding. HIV-2 has been isolated from infected patients in West Africa and it appears to be endemic only in that region. However, HIV-2 also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and ability to cause AIDS. Multiple clinical studies of plasma HIV-1 viral load (expressed as HIV-1 RNA copies/mL of plasma) have shown a clear relationship of HIV-1 RNA copy number to stage of HIV-1 disease and efficacy of anti-HIV-1 therapy. Quantitative HIV-1 RNA level in plasma (ie, HIV-1 viral load) is an important surrogate marker in assessing the risk of disease progression and monitoring response to anti-HIV-1 drug therapy in the routine medical care of individuals living with HIV-1. HIV serologic tests may be unreliable for infants born to HIV-infected mothers. In infants up to 18 months of age, positive serologic test results can be due to the presence of maternal HIV antibodies. Therefore, the U.S. Department of Health and Human Services Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children recommends use of HIV RNA or proviral DNA tests for the detection of HIV infection in infants born to HIV-infected mothers.

Useful For: Diagnosis of HIV-1 infection in individuals with acute or early HIV-1 infection
Diagnosis of HIV-1 infection in infants under 18 months of age born to mothers living with HIV-1
Quantifying plasma HIV-1 RNA levels (viral load) in individuals living with HIV-1: -Before initiating anti-HIV-1 drug therapy (baseline viral load) -Who may have developed HIV-1 drug resistance while on anti-HIV-1 therapy -Who may be noncompliant with anti-HIV-1 drug therapy Monitoring HIV-1 disease progression before or during antiretroviral drug therapy

Interpretation: This assay has a plasma HIV-1 RNA quantification result range of 20 to 10,000,000 copies/mL (1.30-7.00 log copies/mL). An "Undetected" result indicates that the assay was unable to detect HIV-1 RNA in the plasma specimen tested. A result of "<20 copies/mL" indicates that HIV-1 RNA is detected, but the level present is less than the lower quantification limit of this assay. Due to the increased sensitivity of this assay, patients with previously low or undetectable HIV-1 viral load may show increased or detectable viral load with this assay. However, the clinical implications of a viral load below 20 copies/mL remain unclear. Possible causes of such a result include very low plasma HIV-1 viral load present (eg, in the range of 1-19 copies/mL), very early HIV-1 infection (ie, <3 weeks from time of infection), or absence of HIV-1 infection (ie, false-positive). A result of ">10,000,000 copies/mL" with the result comment of "HIV-1 RNA level is >10,000,000 copies/mL (>7.00 log copies/mL). This assay cannot accurately quantify HIV-1 RNA above this level" indicates that HIV-1 RNA is detected, but the level present is above the upper quantification limit of this assay. For the purpose of monitoring patient's response to antiretroviral therapy, the US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents defines virologic failure as a confirmed viral load above 200 copies/mL, which eliminates most cases of viremia resulting from isolated blips or assay variability. Confirmed viral load rebound (ie, >200 copies/mL) on 2 separate tests obtained at least 2 to 4 weeks apart should prompt a careful evaluation of patient's tolerance of current drug therapy, drug-drug interactions, and patient adherence.

Reference Values:

HIV-1 RNA Detection and Quantification, Plasma

Clinical Information: Currently, 2 types of HIV, HIV type 1 (HIV-1) and HIV type 2 (HIV-2), are known to infect humans. HIV-1 has been isolated from patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high-risk for AIDS. Accounting for more than 99% of HIV infection in the world, HIV-1 is transmitted by sexual contact, by exposure to infected blood or blood products, from an infected pregnant woman to fetus in utero or during birth, or from an infected mother to infant via breast-feeding. HIV-2 has been isolated from infected patients in West Africa and it appears to be endemic only in that region. However, HIV-2 also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and ability to cause AIDS. Multiple clinical studies of plasma HIV-1 viral load (expressed as HIV-1 RNA copies/mL of plasma) have shown a clear relationship of HIV-1 RNA copy number to stage of HIV-1 disease and efficacy of anti-HIV-1 therapy. Quantitative HIV-1 RNA level in plasma (ie, HIV-1 viral load) is an important surrogate marker in assessing the risk of disease progression and monitoring response to anti-HIV-1 drug therapy in the routine medical care of HIV-1-infected patients. HIV serologic tests may be unreliable for infants born to HIV-infected mothers. In infants up to 18 months of age, positive serologic test results can be due to the presence of maternal HIV antibodies. Therefore, the United States Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children recommends use of proviral DNA or RNA tests for the detection of HIV infection in infants born to HIV-infected mothers.(1)

Useful For: Diagnosis of HIV-1 infection in individuals with acute or early HIV-1 infection Diagnosis of HIV-1 infection in infants of under 18 months of age born to HIV-1-infected mothers Quantifying plasma HIV-1 RNA levels (viral load) in HIV-1-infected individuals: -Before initiating anti-HIV-1 drug therapy (baseline viral load) -Who may have developed HIV-1 drug resistance while on anti-HIV-1 therapy -Who may be noncompliant with anti-HIV-1 drug therapy Monitoring HIV-1 disease progression while on or off antiretroviral drug therapy

Interpretation: This assay has a plasma HIV-1 RNA quantification result range of 20 to 10,000,000 copies/mL (1.30-7.00 log copies/mL). An "Undetected" result indicates that the assay was unable to detect HIV-1 RNA in the plasma specimen tested. A result of "<20 copies/mL" indicates that HIV-1 RNA is detected, but the level present is less than the lower quantification limit of this assay. Due to the increased sensitivity of this assay, patients with previously low or undetectable HIV-1 viral load may show increased or detectable viral load with this assay. However, the clinical implications of a viral load below 20 copies/mL remain unclear. Possible causes of such a result include very low plasma HIV-1 viral load present (eg, in the range of 1-19 copies/mL), very early HIV-1 infection (ie, less than 3 weeks from time of infection), or absence of HIV-1 infection (ie, false-positive). A result of ">10,000,000 copies/mL" with the result comment of "HIV-1 RNA level is >10,000,000 copies/mL (>7.00 log copies/mL). This assay cannot accurately quantify HIV-1 RNA above this level” indicates that HIV-1 RNA is detected, but the level present is above the upper quantification limit of this assay. For the purpose of monitoring patientâ€™s response to antiretroviral therapy, the US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents defines virologic failure as a confirmed viral load of above 200 copies/mL, which eliminates most cases of viremia resulting from isolated blips or assay variability. Confirmed viral load rebound (ie, >200 copies/mL) on 2 separate tests obtained at least 2 to 4
weeks apart should prompt a careful evaluation of patient's tolerance of current drug therapy, drug-drug interactions, and patient adherence.

**Reference Values:**
Undetected

**Clinical References:**

**HIV-1 RNA Detection and Quantification, Prenatal, Plasma**

**Clinical Information:**
Currently, 2 types of HIV, HIV type 1 (HIV-1) and HIV type 2 (HIV-2), are known to infect humans. HIV-1 has been isolated from patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high-risk for AIDS. Accounting for more than 99% of HIV infection in the world, HIV-1 is transmitted by sexual contact, by exposure to infected blood or blood products, from an infected pregnant woman to fetus in utero or during birth, or from an infected mother to infant via breast-feeding. HIV-2 has been isolated from infected patients in West Africa and it appears to be endemic only in that region. However, HIV-2 also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and ability to cause AIDS. Multiple clinical studies of plasma HIV-1 viral load (expressed as HIV-1 RNA copies/mL of plasma) have shown a clear relationship of HIV-1 RNA copy number to stage of HIV-1 disease and efficacy of anti-HIV-1 therapy. Quantitative HIV-1 RNA level in plasma (ie, HIV-1 viral load) is an important surrogate marker in assessing the risk of disease progression and monitoring response to anti-HIV-1 drug therapy in the routine medical care of HIV-1-infected patients.

**Useful For:**
Diagnosis of HIV-1 infection in pregnant individuals with acute or early HIV-1 infection
Quantifying plasma HIV-1 RNA levels (viral load) in pregnant individuals living with HIV-1: - Before initiating anti-HIV-1 drug therapy (baseline viral load) - Who may have developed HIV-1 drug resistance while on anti-HIV-1 therapy - Who may be noncompliant with anti-HIV-1 drug therapy Monitoring HIV-1 disease progression before or during antiretroviral drug therapy in pregnant individuals

**Interpretation:**
This assay has a plasma HIV-1 RNA quantification result range of 20 to 10,000,000 copies/mL (1.30-7.00 log copies/mL). An "Undetected" result indicates that the assay was unable to detect HIV-1 RNA in the plasma specimen tested. A result of "<20 copies/mL" indicates that HIV-1 RNA is detected, but the level present is less than the lower quantification limit of this assay. Due to the increased sensitivity of this assay, patients with previously low or undetectable HIV-1 viral load may show increased or detectable viral load with this assay. However, the clinical implications of a viral load <20 copies/mL remain unclear. Possible causes of such a result include very low plasma HIV-1 viral load present (eg, in the range of 1-19 copies/mL), very early HIV-1 infection (ie, <3 weeks from time of infection), or absence of HIV-1 infection (ie, false-positive). A result of ">10,000,000 copies/mL" with the result comment of "HIV-1 RNA level is >10,000,000 copies/mL (>7.00 log copies/mL). This assay cannot accurately quantify HIV-1 RNA above this level" indicates that HIV-1 RNA is detected, but the level present is above the upper quantification limit of this assay. For the purpose of monitoring patient's response to antiretroviral therapy, the United States Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents defines virologic failure as a confirmed viral load of above 200 copies/mL, which eliminates most cases of viremia resulting from isolated blips or assay variability. Confirmed viral load rebound (ie, >200 copies/mL) on 2 separate tests obtained at least 2 to 4 weeks apart should prompt a careful evaluation of patient's tolerance of current drug...
therapy, drug-drug interactions, and patient adherence.

**Reference Values:**

Undetected

**Clinical References:**

**HIRGT 65713**

**HIV-1 RNA Quantification with Reflex to HIV-1 Genotypic Drug Resistance to Protease and Reverse Transcriptase Inhibitors, Plasma**

**Clinical Information:** HIV-1 is an RNA virus that infects human host cells and is then converted to complementary DNA (cDNA) by the action of viral reverse transcriptase. HIV-1 is the causative agent of AIDS, a severe, life-threatening condition. Currently, 2 types of HIV: HIV type 1 (HIV-1) and HIV type 2 (HIV-2), are known to infect humans. HIV-1 has been isolated from patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high-risk for AIDS. Accounting for over 99% of HIV infections in the world, HIV-1 is transmitted by sexual contact, by exposure to infected blood or blood products, from an infected pregnant woman to fetus in utero or during birth, or from an infected mother to infant via breast feeding. HIV-2 has been isolated from infected patients in West Africa and it appears to be endemic only in that region. However, HIV-2 also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and ability to cause AIDS. Multiple clinical studies of plasma HIV-1 viral load (expressed as HIV-1 RNA copies/mL of plasma) have shown a clear relationship of HIV-1 RNA copy number to stage of HIV-1 disease and efficacy of anti-HIV-1 therapy. Quantitative HIV-1 RNA level in plasma (ie, HIV-1 viral load) is an important surrogate marker in assessing the risk of disease progression and monitoring response to anti-HIV-1 drug therapy in the routine medical care of HIV-1-infected patients. Studies have identified a number of mutations associated with antiviral resistance. Genotypic analysis allows identification of nucleotide changes associated with HIV drug resistance. When combination therapy fails, genotyping for drug resistance mutations may help direct appropriate changes in antiretroviral therapy and may result in at least a short-term benefit, as evidenced by viral load reduction.

**Useful For:** Quantifying plasma HIV-1 RNA levels (viral load) in individuals living with HIV, including children, followed by identification of genotypic mutations associated with viral resistance to inhibitors of HIV-1 reverse transcriptase and protease Guiding initiation or change of combination antiretroviral therapy in individuals, including children, living with HIV

**Interpretation:** HIRGT: This assay has a plasma HIV-1 RNA quantification result range of 20 to 10,000,000 copies/mL (1.30-7.00 log copies/mL). An "Undetected" result indicates that the assay was unable to detect HIV-1 RNA within the plasma specimen. A result of "<20 IU/mL" indicates that HIV-1 RNA is detected, but the level present is less than the lower quantification limit of this assay. Due to the increased sensitivity of this assay, patients with previously low or undetectable HIV-1 viral load may show increased or detectable viral load with this assay. However, the clinical implications of a viral load below 20 copies/mL remain unclear. Possible causes of such a result include very low plasma HIV-1 viral load present (eg, in the range of 1-19 copies/mL), very early HIV-1 infection (ie, less than 3 weeks from time of infection), or absence of HIV-1 infection (ie, false-positive). A result of ">10,000,000" with the
result comment of "HIV-1 RNA level is >10,000,000 copies/mL (>7.00 log copies/mL). This assay cannot accurately quantify HIV-1 RNA above this level" indicates that HIV-1 RNA is detected, but the level present is above the upper quantification limit of this assay. For the purpose of monitoring patient's response to antiretroviral therapy, the US Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents defines virologic failure as a confirmed viral load of greater than 200 copies/mL, which eliminates most cases of viremia resulting from isolated blips or assay variability. Confirmed viral load rebound (ie, >200 copies/mL) on 2 separate tests obtained at least 2 to 4 weeks apart should prompt a careful evaluation of patient's tolerance of current drug therapy, drug-to-drug interactions, and patient adherence. If the viral load is greater than or equal to 500 copies/mL, genotypic antiviral drug resistance mutation analysis is performed automatically at an additional charge. HIVPR: Codon sequences of the patient's HIV-1 reverse transcriptase and protease genes are compared with those in a database of known antiretroviral drug resistance mutations provided in the assay manufacturer's software application. Results are provided that highlight those codon changes associated with specific drug resistance. These mutations are categorized and reported. "Susceptible (SUSC)" indicates that the genotypic mutations present in patient's HIV-1 strain have not been associated with resistance to the specific drug in question. "Resistant (RESIST)" indicates that genotypic mutations detected have been associated with maximum reduction in susceptibility to the specific drug. "Possible resistance (PR)" indicates that genotypic mutations detected have been associated with maximum reduction in susceptibility to the specific drug and/or intermediate decrease in susceptibility of the virus to the specific drug. "Unable to genotype" result indicates that the sequence data obtained are of poor quality to determine the presence or absence of genotypic resistant mutations in the patient's HIV strain. Probable causes of such poor sequence data include polymorphism in the region of the sequencing primers interfering with primer binding and subsequent sequencing reaction, or low viral load (ie, <500 copies/mL). "Inconclusive" result indicates inability of the assay to reliably determine antiviral resistance because of the presence of PCR inhibitors or ambiguous or incomplete viral target sequences generated from the assay.

**Reference Values:**
Undetected


**HIV-1 RNA Quantification with Reflex to HIV-1 Genotypic Drug Resistance, Plasma**

**Clinical Information:** HIV-1 is an RNA virus that infects human host cells and is then converted to complementary DNA (cDNA) by the action of viral reverse transcriptase. HIV-1 is the causative agent of AIDS, a severe, life-threatening condition. Currently, 2 types of HIV: HIV type 1 (HIV-1) and HIV type 2 (HIV-2), are known to infect humans. HIV-1 has been isolated from patients with AIDS, AIDS-related complex, and asymptomatic infected individuals at high-risk for AIDS. Accounting for over 99% of HIV infections in the world, HIV-1 is transmitted by sexual contact, by exposure to infected blood or blood products, from an infected pregnant woman to fetus in utero or during birth, or from an infected mother to infant via breast feeding. HIV-2 has been isolated from infected patients in West Africa and it appears to be endemic only in that region. However, HIV-2 also has been identified in individuals who have lived in West Africa or had sexual relations with individuals from that
geographic region. HIV-2 is similar to HIV-1 in its morphology, overall genomic structure, and ability to cause AIDS. Multiple clinical studies of plasma HIV-1 viral load (expressed as HIV-1 RNA copies/mL of plasma) have shown a clear relationship of HIV-1 RNA copy number to stage of HIV-1 disease and efficacy of anti-HIV-1 therapy. Quantitative HIV-1 RNA level in plasma (ie, HIV-1 viral load) is an important surrogate marker in assessing the risk of disease progression and monitoring response to anti-HIV-1 drug therapy in the routine medical care of HIV-1-infected patients. Studies have identified a number of mutations associated with antiviral resistance. Genotypic analysis allows identification of nucleotide changes associated with HIV drug resistance. When combination therapy fails, genotyping for drug resistance mutations may help direct appropriate changes in antiretroviral therapy and may result in at least a short-term benefit, as evidenced by viral load reduction.

**Useful For:** Detecting and quantifying plasma HIV-1 RNA levels (viral load) in HIV-1-infected patients, followed by genotypic determination of viral resistance to anti-HIV drugs Guiding initiation or change of antiretroviral treatment regimens

**Interpretation:** HIV-1 Detection and Quantification: This assay has a plasma HIV-1 RNA quantification result range of 20 to 10,000,000 copies/mL (1.30-7.00 log copies/mL). An "Undetected" result indicates that the assay was unable to detect HIV-1 RNA within the plasma specimen. A result of "<20 IU/mL" indicates that HIV-1 RNA is detected, but the level present is less than the lower quantification limit of this assay. Due to the increased sensitivity of this assay, patients with previously low or undetectable HIV-1 viral load may show increased or detectable viral load with this assay. However, the clinical implications of a viral load below 20 copies/mL remain unclear. Possible causes of such a result include very low plasma HIV-1 viral load present (eg, in the range of 1-19 copies/mL), very early HIV-1 infection (ie, <3 weeks from time of infection), or absence of HIV-1 infection (ie, false-positive). A result of ">10,000,000" with the result comment of "HIV-1 RNA level is >10,000,000 copies/mL (>7.00 log copies/mL). This assay cannot accurately quantify HIV-1 RNA above this level" indicates that HIV-1 RNA is detected, but the level present is above the upper quantification limit of this assay. For the purpose of monitoring patient's response to antiretroviral therapy, the US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents defines virologic failure as a confirmed viral load above 200 copies/mL, which eliminates most cases of viremia resulting from isolated blips or assay variability. Confirmed viral load rebound (ie, >200 copies/mL) on 2 separate tests obtained at least 2 to 4 weeks apart should prompt a careful evaluation of patient's tolerance of current drug therapy, drug-to-drug interactions, and patient adherence. Genotypic anti-HIV-1 drug resistance mutation analysis is performed automatically at an additional charge if the viral load is 500 copies/mL or above. Sequence data of the patient's viral strain is compared with those in a database of known drug resistance mutations. Results are provided that highlight those codon changes associated with specific drug resistance. These mutations are categorized and reported. HIV-1 Genotypic Drug Resistance Analysis: "Susceptible" indicates that the genotypic mutations present in patient's HIV-1 strain have not been associated with resistance to the specific drug in question. "Resistant" indicates that genotypic mutations detected have been associated with maximum reduction in susceptibility to the specific drug. "Possible resistance" indicates that genotypic mutations detected have been associated with 1 or both of the following outcomes: -Diminished virologic response in some, but not all, patients having virus with these mutations -Intermediate decrease in susceptibility of the virus to the specific drug "Unable to genotype" indicates that the sequence data obtained are of poor quality to determine the presence or absence of genotypic resistant mutations in the patient's HIV strain. Possible causes of such poor sequence data include polymorphism in the region of the sequencing primers interfering with primer binding and subsequent sequencing reaction. "Inconclusive" indicates inability of the assay to reliably determine antiviral resistance because of either low HIV-1 viral load (ie, <500 copies/mL) or ambiguous or incomplete viral target sequences generated from the assay.

**Reference Values:**

Undetected

HIV-2 Antibody Confirmation, Serum

**Clinical Information:** Human immunodeficiency virus type 2 (HIV-2) is a lentivirus, a retrovirus in the same genus (Lentiviridae) as HIV-1. It was first isolated in 1986 in West Africa, where it is currently endemic. As of June 2010, CDC has reported a total of 166 cases that met the CDC case definition of HIV-2 infection in the United States. Most of these cases were found in the northeastern United States, and the majority had a West African origin or connection. Compared to HIV-1 infection, HIV-2 infection is associated with slower rate of progression, low viral load (which may not be reliably measurable with current methods), slower rates of decline in CD4 cell count, and lower rates of transmission (sexually or vertically). Up to 95% of HIV-2-infected individuals are long-term nonprogressors, and individuals with undetectable HIV-2 viral load have similar survival rates as that of the uninfected population. However, HIV-2 does cause immunosuppression as well as AIDS with the same signs, symptoms, and opportunistic infections seen in HIV-1. Due to the rarity of HIV-2, there are scant data from controlled trials to inform management decisions. Although there are several FDA-approved screening assays to detect both combined HIV-1 and HIV-2 antibodies or HIV-2 antibodies alone, currently there is only 1 FDA-approved supplemental (confirmatory) HIV-2 serologic assay for clinical use in the United States. Interpretation of visible band patterns is complicated due to the significant cross-reactivity between HIV-1 and HIV-2 antibodies in this assay.

**Useful For:** Confirmation of the presence of HIV-2 antibodies in patients with repeatedly reactive combined HIV-1 and HIV-2 antibody or HIV-2 antibody-only screening test results Diagnosis of HIV-2 infection

**Interpretation:** Negative results for HIV-2 antibodies usually indicate absence of HIV-2 infection. However, in patients with reactive initial combined HIV-1/-2 antigen and antibody test results, such negative results do not rule-out acute or early HIV-2 infection. If acute or early HIV-2 infection is suspected, detection of HIV-2 DNA/RNA RNA (FHV2Q / HIV-2 DNA/RNA Qualitative Real-Time PCR) is recommended, based on patient’s clinical and epidemiologic exposure history. Positive HIV-2 antibody results indicate the presence of HIV-2 infection. Verification of a first-time positive test result is recommended for the diagnosis of HIV-2 infection, by submitting a plasma specimen for HIV-2 DNA/RNA (FHV2Q). Indeterminate results HIV-2 antibodies may be due to acute HIV-1 infection or very early HIV-2 infection (in individuals with risk factors) submitted for detection of HIV-2 DNA/RNA (FHV2Q), depending on the epidemiologic exposure history.

**Reference Values:**
Negative

This confirmatory assay should be ordered only on specimens that are reactive by an HIV-2 antibody screening immunoassay.

**Clinical References:**
**HIV-2 DNA/RNA Qualitative Real-Time PCR**

Reference Values:
Reference Range: Not Detected

**HLA A High Resolution**

Reference Values:
Testing is complete. Final report has been sent to the referring laboratory.

**HLA B High Resolution**

Reference Values:
Testing is complete. Final report has been sent to the referring laboratory.

**HLA C High Resolution**

Reference Values:
Testing is complete. Final report has been sent to the referring laboratory.

**HLA Class I Molecular Typing Disease Association**

Clinical Information: Human leukocyte antigens (HLA) are regulators of the immune response that play a key role in transplantation. HLA class I typing is most frequently applicable to organ transplant donor/recipient matching, provision of HLA-matched platelets for alloimmunized refractory patients, and for a small number of disease associations. Class I HLA antigens include A, B, and C loci. This assay is designed to provide low-to-medium resolution for HLA class I typing (A, B, C). Low-to-medium resolution defines the typing at the antigen level. This is in contrast to high-resolution typing, which defines typing at the allele (molecular) level and is used primarily for typing donor/recipient pairs for unrelated bone marrow transplantation.

Useful For: Determining class I HLA antigens on specimens for transplant candidates and their donors or those who have become refractory to platelet transfusions

Interpretation: Interpretation depends on the rationale for ordering the test. Assessments of acceptable donor/recipient matches are made on a case-by-case basis.

Reference Values:
Not applicable

Clinical References:

**HLA Class II Molecular Typing Disease Association**

Clinical Information: Human leukocyte antigens (HLA) are regulators of the immune response that play a key role in transplantation. Sequence-specific oligonucleotides are designed to provide low-to-medium resolution for HLA Class II (DR and DQ) typing. Low-to-medium resolution defines the typing at the antigen level. This is in contrast to high-resolution typing, which defines typing at the allele (molecular) level and is used primarily for typing donor-recipient pairs for unrelated bone marrow transplantation.
**Useful For:** Determining HLA Class II compatibility on specimens from bone marrow and solid organ transplant candidates and their donors

**Interpretation:** Interpretation depends on the rationale for ordering the test. Assessments of acceptable donor/recipient matches are made on a case-by-case basis.

**Reference Values:**
Not applicable

**Clinical References:**

**HLA-B 5701 Genotype, Abacavir Hypersensitivity, Blood**

**Clinical Information:** The human leukocyte antigen (HLA) genes help the immune system recognize and respond to foreign substances (such as viruses and bacteria). The HLA-B gene encodes a class I HLA molecule in the major histocompatibility complex (MHC), which acts by presenting peptides to immune cells. There are more than 1,500 different HLA-B alleles identified, one of which is the HLA-B*57:01 allele. Frequency of the HLA-B*57:01 allele varies with ethnicity, with a frequency of 6% to 7% in European populations, and up to 20% in Southwest Asian populations. The HLA-B*57:01 allele has been associated with hypersensitivity to abacavir, a highly effective nucleoside analog reverse-transcriptase inhibitor used to treat HIV infection and AIDS. Per the Clinical Pharmacogenomics Implementation Consortium (CPIC) dosing guidelines for abacavir and HLA-B, individuals who are positive for the HLA-B*57:01 allele are at an increased risk for abacavir hypersensitivity and it is not recommended for use in treating these individuals. Hypersensitivity reactions, which generally occur during the first 6 weeks of treatment, are often nonspecific and include skin rashes, gastrointestinal symptoms (eg, nausea, vomiting, diarrhea, and abdominal pain), and respiratory symptoms. Fatalities have been reported with abacavir hypersensitivity. Prospective testing for the HLA-B*57:01 genotype and excluding HLA-B*57:01-positive individuals from treatment with abacavir decreases the incidence of abacavir hypersensitivity. See Abacavir Hypersensitivity Testing and Initial Patient Management Algorithm in Special Instructions. Pazopanib is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma and advanced soft tissue sarcoma who have received prior chemotherapy. In clinical trials with pazopanib, hepatotoxicity was observed, manifested as increases in serum transaminases such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin. This hepatotoxicity can be severe and fatal. Patients older than 65 years are at greater risk for hepatotoxicity. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks). HLA-B*57:01 carriers who are taking pazopanib are at increased risk of elevated ALT levels.(1,2) According to the FDA label for pazopanib, in an analysis of data from 31 clinical studies of pazopanib administered as either monotherapy or in combination with other agents, elevation in ALT to levels greater than 3 times the upper limit of normal occurred in 32% (42/133) of HLA-B*57:01 allele carriers as compared to 19% (397/2101) of noncarriers. Furthermore, elevation in ALT to levels greater than 5 times the upper limit of normal occurred in 19% (25/133) of HLA-B*57:01 allele carriers and in 10% (213/2101) of noncarriers. All patients taking pazopanib should have hepatic function monitored, regardless of HLA-B*57:01 carrier status, and administration of pazopanib should be interrupted, reduced, or discontinued according to recommendations in the FDA label if hepatic function is impaired. UGT1A1 genotype is also relevant to pazopanib-induced hyperbilirubinemia and testing may also be warranted. See U1A1V / UDP-Glucuronosyl Transferase 1A1 TA Repeat Genotype, UGT1A1.

**Useful For:** Identifying individuals with an increased risk of hypersensitivity reactions to abacavir, based on the presence of the human leukocyte antigen HLA-B*57:01 allele. Identifying individuals taking pazopanib who have an increased risk of elevated alanine aminotransferase levels based on the presence of the human leukocyte antigen HLA-B*57:01 allele.
**Interpretation:** Positivity for human leukocyte antigen allele HLA-B*57:01 confers high risk for hypersensitivity to abacavir and higher risk of elevated alanine aminotransferase levels in patient taking pazopanib. See Abacavir Hypersensitivity Testing and Initial Patient Management Algorithm in Special Instructions. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
Negative
An interpretive report will be provided.

**Clinical References:**

**HLA-B 5701 Genotype, Abacavir Hypersensitivity, Saliva**

**Clinical Information:** The human leukocyte antigen (HLA) genes help the immune system recognize and respond to foreign substances (such as viruses and bacteria). The HLA-B gene encodes a class 1 HLA molecule in the major histocompatibility complex (MHC), which acts by presenting peptides to immune cells. There are more than 1,500 different HLA-B alleles identified, one of which is the HLA-B*57:01 allele. Frequency of the HLA-B*57:01 allele varies with ethnicity, with a frequency of 6% to 7% in European populations, and up to 20% in Southwest Asian populations. The HLA-B*57:01 allele has been associated with hypersensitivity to abacavir, a highly effective nucleoside analog reverse-transcriptase inhibitor used to treat HIV infection and AIDS. Per the Clinical Pharmacogenomics Implementation Consortium (CPIC) dosing guidelines for abacavir and HLA-B, individuals who are positive for the HLA-B*57:01 allele are at an increased risk for abacavir hypersensitivity and it is not recommended for use in treating these individuals. Hypersensitivity reactions, which generally occur during the first 6 weeks of treatment, are often nonspecific and include skin rashes, gastrointestinal symptoms (eg, nausea, vomiting, diarrhea, and abdominal pain), and respiratory symptoms. Fatalities have been reported with abacavir hypersensitivity. Prospective testing for the HLA-B*57:01 genotype and excluding HLA-B*57:01-positive individuals from treatment with abacavir decreases the incidence of abacavir hypersensitivity. See Abacavir Hypersensitivity Testing and Initial Patient Management Algorithm in Special Instructions. Pazopanib is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma and advanced soft tissue sarcoma who have received prior chemotherapy. In clinical trials with pazopanib, hepatotoxicity was observed, manifested as increases in serum transaminases such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin. This hepatotoxicity can be severe and fatal. Patients older than 65 years are at greater risk for hepatotoxicity. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks). HLA-B*57:01 carriers who are taking pazopanib are at increased risk of elevated ALT levels.2. According to the FDA label for pazopanib, in an analysis of data from 31 clinical studies of pazopanib administered as either monotherapy or in combination with other agents, elevation in ALT to levels greater than 3 times the upper limit of normal occurred in 32% (42/133) of HLA-B*57:01 allele carriers as compared to 19% (397/2101) of non-carriers. Furthermore, elevation in ALT to levels greater than 5 times the upper limit of normal occurred in 19% (25/133) of HLA-B*57:01
allele carriers and in 10% (213/2101) of non-carriers. All patients taking pazopanib should have hepatic function monitored, regardless of HLA-B*57:01 carrier status, and administration of pazopanib should be interrupted, reduced, or discontinued according to recommendations in the FDA label if hepatic function is impaired. UGT1A1 genotype is also relevant to pazopanib-induced hyperbilirubinemia and testing may also be warranted. See U1A1V / UDP-Glucuronosyl Transferase 1A1 TA Repeat Genotype, UGT1A1.

**Useful For:** Identifying individuals with an increased risk of hypersensitivity reactions to abacavir, based on the presence of the HLA-B*57:01 allele Identifying individuals taking pazopanib who have an increased risk of elevated alanine aminotransferase levels based on the presence of the human leukocyte antigen HLA-B*57:01 allele Genotyping patients who prefer not to have venipuncture done

**Interpretation:** Positivity for human leukocyte antigen allele HLA-B*57:01 confers high risk for hypersensitivity to abacavir and higher risk of elevated alanine aminotransferase levels in patient taking pazopanib. See Abacavir Hypersensitivity Testing and Initial Patient Management Algorithm in Special Instructions. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
Negative
An interpretive report will be provided.

**Clinical References:**

**HLA-B*5801 Genotype, Allopurinol Hypersensitivity, Blood**

**Clinical Information:** The human leukocyte antigen (HLA) genes help the immune system recognize and respond to foreign substances (such as viruses and bacteria). The HLA-B gene encodes a class 1 HLA molecule in the major histocompatibility complex (MHC), which acts by presenting peptides to immune cells. There are more than 1,500 different HLA-B alleles identified, one of which is the HLA-B*58:01 allele. Frequency of the HLA-B*58:01 allele varies with ethnicity, with a frequency of 6% to 7% in Asian populations, and 1% in Caucasian populations. Allopurinol is a drug widely used for hyperuricemia-related diseases such as gout, Lesch-Nyhan syndrome, and recurrent urate kidney stones. However, this drug is one of the most common causes of severe cutaneous adverse reactions (SCAR), an umbrella term encompassing drug hypersensitivity syndrome, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). These reactions have a reported mortality rate of 20% to 25%. For individuals taking allopurinol, the presence of the HLA-B*58:01 allele has been strongly associated with allopurinol-induced SCAR. Guidelines from the Clinical Pharmacogenomics Implementation Consortium (CPIC) recommend HLA-B*58:01 genotyping be performed when considering prescribing allopurinol, and that allopurinol should not be prescribed to patients who test positive for the allele due to the increased risk of SCAR.(1) In addition, guidelines developed by the 2012 American College of Rheumatology for Management of Gout recommend that HLA-B*58:01 testing should be considered in select patient subpopulations at an elevated risk for allopurinol-induced SCAR. Those of Korean descent, especially those with stage 3 or higher chronic kidney disease, or of...
Useful For: Identifying individuals with an increased risk of severe cutaneous adverse reactions to allopurinol based on the presence of the human leukocyte antigen HLA-B*58:01 allele

Interpretation: Positivity for HLA-B*58:01 confers increased risk for hypersensitivity to allopurinol. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values:
An interpretive report will be provided.

Clinical References:
**LY27B**

**HLA-B27, Blood**

**Clinical Information:** This major histocompatibility coded class I antigen is associated with ankylosing spondylitis, juvenile rheumatoid arthritis, and Reiter syndrome. The mechanism of the association is not understood but probably is that of linkage disequilibrium. There is an increased prevalence of HLA-B27 in certain rheumatic diseases, particularly ankylosing spondylitis. Studies have demonstrated that the B*27:06 allele, which is present in a small percentage of individuals of Asian ethnicity, may not be associated with ankylosing spondylitis.

**Useful For:** Assisting in the diagnostic process of ankylosing spondylitis, juvenile rheumatoid arthritis, and Reiter syndrome

**Interpretation:** Approximately 8% of the normal population carries the HLA-B27 antigen. HLA-B27 is present in approximately 89% of patients with ankylosing spondylitis, 79% of patients with Reiter syndrome, and 42% of patients with juvenile rheumatoid arthritis. However, lacking other data, it is not diagnostic for these disorders.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**HMB45 Immunostain, Technical Component Only**

**Clinical Information:** The HMB45 immunostain identifies an antigen that is associated with a premelanosomal glycoprotein found in activated and neoplastic melanocytes. Most melanomas (approximately 90%) react with HMB45. HMB45 staining is cytoplasmic and is usually diffuse, but may be focal. Benign nevi (moles), and other tumors that have melanin production (such as peripheral nerve sheath tumors), also stain positively.

**Useful For:** Aids in the identification of activated and neoplastic melanocytes

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**HMBSZ**

**HMBS Gene, Full Gene Analysis**

**Clinical Information:** Hydroxymethylbilane synthase (HMBS) deficiency is an autosomal dominant disorder with incomplete penetrance that can present as acute intermittent porphyria (AIP). The most common clinical presentation of AIP is abdominal pain. Acute attacks can include vomiting, diarrhea, constipation, urinary retention, acute episodes of neuropathic symptoms, psychiatric symptoms, seizures, respiratory paralysis, tachycardia, and hypertension. Respiratory paralysis can progress to coma and death. HMBS deficiency can also be without clinical or biochemical manifestations. Acute attacks may be prevented by avoiding both endogenous and exogenous triggers. These triggers include porphyrigenic drugs, hormonal contraceptives, fasting, alcohol, tobacco and cannabis. The measurement of porphobilinogen deaminase (PBG-D) enzyme activity in erythrocytes facilitates detection of AIP during latent periods, and also confirms a biochemical diagnosis during acute episodes. However, a normal result does not completely exclude a diagnosis of HMBS deficiency/AIP. The preferred diagnostic test is molecular genetic testing of the HMBS gene.

**Useful For:** Confirming a diagnosis of hydroxymethylbilane synthase deficiency/acute intermittent porphyria

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.


**HCMM**

**Homocysteine (Total), Methylmalonic Acid, and Methylcitric Acid, Blood Spots**

**Clinical Information:** Homocystinuria is an autosomal recessive disorder caused by a deficiency of the enzyme cystathionine beta-synthase. The incidence of homocystinuria is approximately 1 in 200,000 to 335,000 live births. Classical homocystinuria is characterized by a normal presentation at birth followed by failure to thrive and developmental delay. Untreated homocystinuria can lead to ophthalmological problems, mental retardation, seizures, thromboembolic episodes, and skeletal abnormalities. The biochemical phenotype is characterized by increased plasma concentrations of methionine and homocysteine (free and total) along with decreased concentrations of cystine. Methylmalonic acidemia (MMA) and propionic acidemia (PA) are defects of propionate metabolism caused by deficiencies in methylmalonyl-CoA mutase and propionyl-CoA carboxylase, respectively. The clinical phenotype includes vomiting, hypotonia, lethargy, apnea, hypothermia, and coma. The
biochemical phenotype for MMA includes elevations of propionyl carnitine, methylmalonic acid, and methylcitric acid. Patients with PA will have elevations of propionyl carnitine and methylcitric acid with normal methylmalonic acid concentrations as the enzymatic defect is upstream of methylmalonic-CoA mutase. Newborn screening for inborn errors of methionine and propionic acid metabolism relies on elevations of methionine and propionyl carnitine. These analytes are not specific for these conditions and are prone to false-positive results, leading to increased cost, stress, and anxiety for families who are subjected to follow-up testing. Homocysteine, methylmalonic acid, and methylcitric acid are more specific markers for inborn errors of methionine and propionic acid metabolism. Molecular genetic testing can be used to confirm a biochemical diagnosis for homocystinuria, methylmalonic acidemia, and propionic acidemia.

**Useful For:** Second-tier assay of newborn screening specimens when abnormal propionyl carnitine or methionine concentrations are identified in a primary newborn screen

**Interpretation:** Elevated homocysteine, methylcitric acid, or methylmalonic acid concentrations are indicative of an underlying metabolic disorder. In a Mayo study that analyzed 200 unaffected neonates, clear clinical discrimination was observed when compared to patients with defects of propionate or methionine metabolism. The 99.5 percentile, determined from the analysis of 200 dried blood spots of unaffected controls, for methylmalonic acid (MMA), methylcitric acid (MCA), and homocysteine (HCY), are 1.58 nmol/mL, 0.62 nmol/mL, and 9.9 nmol/mL, respectively, providing clear clinical discrimination from patients with defects of propionate or methionine metabolism (eg, methylmalonic acidemia: MMA=31.9 nmol/mL; propionic acidemia: MCA=12.8 nmol/mL; homocystinuria: HCY=189 nmol/mL).

**Reference Values:**
- Homocysteine: <15.0 nmol/mL
- Methylmalonic acid: <5.0 nmol/mL
- Methylcitric acid: <1.0 nmol/mL

An interpretive report will also be provided.

**Clinical References:**

**Homocysteine, Total, Plasma**

**Clinical Information:** Homocysteine is an intermediary in the sulfur-amino acid metabolism pathways, linking the methionine cycle to the folate cycle. Inborn errors of metabolism that lead to homocysteinemia or homocystinuria include cystathionine beta-synthase deficiency (homocystinuria) and various defects of methionine remethylation. Genetic defects in vitamin cofactors (vitamin B6, B12, and folate) and nutritional deficiency of B12 and folate also lead to abnormal homocysteine accumulation. Homocysteine concentration is an indicator of acquired folate or cobalamin deficiency, and is a contributing factor in the pathogenesis of neural tube defects. Homocysteine also was thought to be an independent predictor of cardiovascular disease (atherosclerosis, heart disease, thromboembolism), as early observational studies prior to 2000 linked homocysteine to cardiovascular risk and morbidity and mortality. However, following FDA-mandated folic acid supplementation in 1998, homocysteine concentrations decreased by approximately 10% without a similar change in cardiovascular or ischemic events. Currently, the use of homocysteine for assessment of cardiovascular risk is uncertain and controversial. Based on several meta-analyses, at present, homocysteine may be regarded as a weak risk factor for coronary heart disease, and there is a lack of direct causal relationship between hyperhomocysteinemia and cardiovascular disease. It is most likely an indicator of poor
lifestyle and diet. This test should be used in conjunction with plasma amino acids and urine organic acids to aid in the biochemical screening for primary and secondary disorders of methionine metabolism.

**Useful For:** An aid for screening patients suspected of having an inherited disorder of methionine metabolism including: -Cystathionine beta-synthase deficiency (homocystinuria) -Methylenetetrahydrofolate reductase deficiency (MTHFR) and its thermolabile variants -Methionine synthase deficiency -Cobalamin (Cbl) metabolism: -Combined methyl-Cbl and adenosyl-Cbl deficiencies: Cbl C2, Cbl D2, and Cbl F3 deficiencies -Methyl-Cbl specific deficiencies: Cbl D-Var1, Cbl E, and Cbl G deficiencies -Transcobalamin II deficiency: -Adenosylhomocysteinase (AHCY) deficiency -Glycine N-methyltransferase (GNMT) deficiency -Methionine adenosyltransferase (MAT) I/III deficiency

**Interpretation:** Homocysteine concentrations >13 mcg/mL are considered abnormal in patients evaluated for suspected nutritional deficiencies (B12, folate) and inborn errors of metabolism. Measurement of methylmalonic acid (MMA) distinguishes between B12 (cobalamin) and folate deficiencies, as MMA is only elevated in B12 deficiency. Response to dietary treatment can be evaluated by monitoring plasma homocysteine concentrations over time. Homocysteine concentrations ≤10 mcg/mL are desirable when utilized for cardiovascular risk.

**Reference Values:**
Adults: ≤13 mcg/mL
Reference values apply to fasting specimens only.

**Clinical References:**

**Homocysteine, Total, Serum**

**Clinical Information:** Homocysteine is an intermediary in the sulfur-amino acid metabolism pathways, linking the methionine cycle to the folate cycle. Inborn errors of metabolism that lead to homocysteinemia or homocysteinuria include cystathionine beta-synthase deficiency (homocystinuria) and various defects of methionine re-methylation. Genetic defects in vitamin cofactors (vitamin B6, B12, and folate) and nutritional deficiency of B12 and folate also lead to abnormal homocysteine accumulation. Homocysteine concentration is an indicator of acquired folate or cobalamin deficiency, and is a contributing factor in the pathogenesis of neural tube defects. Homocysteine also was thought to be an independent predictor of cardiovascular disease (atherosclerosis, heart disease, thromboembolism), as early observational studies prior to 2000 linked homocysteine to cardiovascular risk and morbidity and mortality. However, following FDA-mandated folic acid supplementation in 1998, homocysteine concentrations decreased by approximately 10% without a similar change in cardiovascular or ischemic events. Currently, the use of homocysteine for assessment of cardiovascular risk is uncertain and controversial. Based on several meta-analyses, at present, homocysteine may be regarded as a weak risk factor for coronary heart disease, and there is a lack of direct causal relationship between hyperhomocysteinemia and cardiovascular disease. It is most likely an indicator of poor lifestyle and diet. This test should be used in conjunction with plasma amino acids and urine organic acids to aid in the biochemical screening for primary and secondary disorders of methionine metabolism.

**Useful For:** An aid for screening patients suspected of having an inherited disorder of methionine metabolism including: -Cystathionine beta-synthase deficiency (homocystinuria) -Methylenetetrahydrofolate reductase deficiency (MTHFR) and its thermolabile variants -Methionine synthase deficiency -Cobalamin (Cbl) metabolism: -Combined methyl-Cbl and adenosyl-Cbl deficiencies: Cbl C2, Cbl D2, and Cbl F3 deficiencies -Methyl-Cbl specific deficiencies: Cbl D-Var1, Cbl E, and Cbl G deficiencies -Transcobalamin II deficiency: -Adenosylhomocysteinase (AHCY) deficiency -Glycine N-methyltransferase (GNMT) deficiency -Methionine adenosyltransferase (MAT) I/III deficiency
deficiencies - Transcobalamin II deficiency - Adenosylhomocysteinase (AHCY) deficiency - Glycine N-methyltransferase (GNMT) deficiency - Methionine adenosyltransferase (MAT) I/III deficiency

**Interpretation:** Homocysteine concentrations >13 mcml/L are considered abnormal in patients evaluated for suspected nutritional deficiencies (B12, folate) and inborn errors of metabolism. Measurement of methylmalonic acid (MMA) distinguishes between B12 (cobalamin) and folate deficiencies, as MMA is only elevated in B12 deficiency. Response to dietary treatment can be evaluated by monitoring serum homocysteine concentrations over time. Homocysteine concentrations < or =10 mcml/L are desirable when utilized for cardiovascular risk.

**Reference Values:**
Adults: < or =13 mcml/L
Reference values apply to fasting specimens only.

**Clinical References:**

### HCYSU
80378

**Homocysteine, Total, Urine**

**Clinical Information:** To be used in conjunction with plasma amino acids and urine organic acids to aid in the biochemical screening for primary and secondary disorders of methionine metabolism. Homocysteinuria is an intermediary in the sulfur-amino acid metabolism pathways, linking the methionine cycle to the folate cycle. Inborn errors of metabolism that lead to homocysteinuria/uria include cystathionine beta-synthase deficiency (homocystinuria) and various defects of methionine re-methylation. Homocysteine also was thought to be an independent predictor of cardiovascular disease (atherosclerosis, heart disease, thromboembolism), as early observational studies prior to 2000 linked homocysteine to cardiovascular risk and morbidity and mortality. However, following FDA-mandated folic acid supplementation in 1998, homocysteine concentrations decreased by approximately 10% without a similar change in cardiovascular or ischemic events. Currently, the use of homocysteine for assessment of cardiovascular risk is uncertain and controversial. Based on several meta-analyses, at present, homocysteine may be regarded as a weak risk factor for coronary heart disease, and there is a lack of direct causal relationship between hyperhomocysteinemia and cardiovascular disease. It is most likely an indicator of poor lifestyle and diet.

**Useful For:** As an aid for screening patients suspected of having an inherited disorder of methionine metabolism including: - Cystathionine beta-synthase deficiency (Homocystinuria) - Methyltetrahydrofolate reductase deficiency (MTHFR) and its thermolabile variants: - Methionine synthase deficiency - Cobalamin (Cbl) Metabolism: - Combined Methyl-Cbl and Adenosyl-Cbl deficiencies: Cbl C2, Cbl D2 and Cbl F3 deficiencies - Methionyl-Cbl specific deficiencies: Cbl D-Var1, Cbl E and Cbl G deficiencies - Transcobalamin II deficiency: - Adenosylhomocysteinase: AHCY deficiency - Glycine N-methyltransferase: GNMT deficiency - Methionine Adenosyltransferase I/III Deficiency: MAT I/III deficiency As a (weak) indicator of cardiovascular risk

**Interpretation:** Hyperhomocysteinuria could be caused by either genetic or nutritional factors. While the highest levels are characteristic of classic homocystinuria, there are no reliable cut-offs to differentiate between genetic or dietary causes of elevated homocysteine (Hcy) levels. In our experience, very high Hcy levels have been seen in some patients with cystathionine beta-synthase deficiency. Hcy levels >9 mcml/g creatinine are considered abnormal in patients under evaluation for cardiovascular or neurovascular disease.

**Reference Values:**
Adults: 0-9 mcml/g creatinine


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**Homovanillic Acid (HVA), 24 Hour, Urine**

**Clinical Information:** Homovanillic acid (HVA) and other catecholamine metabolites (vanillylmandelic acid [VMA] and dopamine) are typically elevated in patients with catecholamine-secreting tumors (eg, neuroblastoma, pheochromocytoma, and other neural crest tumors). HVA and VMA levels may also be useful in monitoring patients who have been treated as a result of the above-mentioned tumors. HVA levels may also be altered in disorders of catecholamine metabolism; monoamine oxidase-A deficiency can cause decreased urinary HVA values, while a deficiency of dopamine beta-hydrolase (the enzyme that converts dopamine to norepinephrine) can cause elevated urinary HVA values.

**Useful For:** Screening children for catecholamine-secreting tumors with a 24-hour urine collection when requesting homovanillic acid only Monitoring neuroblastoma treatment Screening patients with possible inborn errors of catecholamine metabolism

**Interpretation:** Vanillylmandelic acid (VMA) and/or homovanillic acid (HVA) concentrations are elevated in over 90% of patients with neuroblastoma; both tests should be performed. A positive test could be due to a genetic or nongenetic condition. Additional confirmatory testing is required. A normal result does not exclude the presence of a catecholamine-secreting tumor. Elevated HVA values are suggestive of a deficiency of dopamine beta-hydrolase, a neuroblastoma, a pheochromocytoma, or may reflect administration of L-dopa. Decreased urinary HVA values may suggest monoamine oxidase-A deficiency.

**Reference Values:**

- <1 year: <35.0 mg/g creatinine
- 1 year: <30.0 mg/g creatinine
- 2-4 years: <25.0 mg/g creatinine
- 5-9 years: <15.0 mg/g creatinine
- 10-14 years: <9.0 mg/g creatinine
- > or =15 years (adults): <8 mg/24 hours


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**Homovanillic Acid (HVA), Random, Urine**

**Clinical Information:** Homovanillic acid (HVA) and other catecholamine metabolites (vanillylmandelic acid [VMA] and dopamine) are typically elevated in patients with catecholamine-secreting tumors (eg, neuroblastoma, pheochromocytoma, and other neural crest tumors). HVA and VMA levels may also be useful in monitoring patients who have been treated as a result of the above-mentioned tumors. HVA levels may also be altered in disorders of catecholamine metabolism; monoamine oxidase-A deficiency can cause decreased urinary HVA values, while a deficiency of
dopamine beta-hydrolase (the enzyme that converts dopamine to norepinephrine) can cause elevated urinary HVA values.

**Useful For:** Screening children for catecholamine-secreting tumors with a random urine collection when requesting homovanillic acid only Monitoring neuroblastoma treatment Screening patients with possible inborn errors of catecholamine metabolism

**Interpretation:** Vanillylmandelic acid and/or homovanillic acid (HVA) concentrations are elevated in over 90% of patients with neuroblastoma; both tests should be performed. A positive test could be due to a genetic or nongenetic condition. Additional confirmatory testing is required. A normal result does not exclude the presence of a catecholamine-secreting tumor. Elevated HVA values are suggestive of a deficiency of dopamine beta-hydrolase, a neuroblastoma, a pheochromocytoma, or may reflect administration of L-dopa. Decreased urinary HVA values may suggest monoamine oxidase-A deficiency.

**Reference Values:**

- <1 year: <35.0 mg/g creatinine
- 1 year: <30.0 mg/g creatinine
- 2-4 years: <25.0 mg/g creatinine
- 5-9 years: <15.0 mg/g creatinine
- 10-14 years: <9.0 mg/g creatinine
- > or =15 years (adults): <8.0 mg/g creatinine

**Clinical References:**


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**Honey, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

Current as of October 11, 2018 2:20 pm CDT

HBV 82551

Honeybee Venom, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.
Hop Fruit, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.
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**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


**HORS 82874 Horse Dander, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
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Reference values apply to all ages.


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**HSPR 82134**

**Horse Serum Proteins, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>3.50-17.4</td>
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Horsefly/Stablefly, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tbody>
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Horseradish (Armoracia rusticana/A. lapathifolia) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

House Dust Mites/Dermatophagoides farinae, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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House Dust Mites/Dermatophagoides pteronyssinus, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from...
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Reference values apply to all ages.


**House Dust Panel**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm
sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**House Dust/Greer Lab, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>Equivocal</td>
</tr>
</tbody>
</table>

House Dust/H-S Lab, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.

**HOXB13 Mutation Analysis (G84E)**

**Clinical Information:** The HOXB13 gene is a homeobox transcription factor involved in normal prostate development and is a key determinant in response to androgens. Recently, a novel germline mutation in the HOXB13 gene, G84E, has been found to be associated with an up to 3- to 5-fold increased risk of prostate cancer. The G84E mutation has been shown to be overrepresented in the disease population, and carriers of the G84E mutation may develop prostate cancer at an earlier age than noncarriers. However, the G84E mutation has been seen in both family members with prostate cancer and in healthy relatives, indicating reduced penetrance. Also, in families carrying the G84E mutation, prostate cancer has been reported in nonmutation carriers.

**Useful For:** Determining whether the clinical phenotype of prostate cancer is due to the G84E mutation in the HOXB13 gene in the affected individual. Predictive testing and familial risk assessment when the G84E mutation in the HOXB13 gene has been identified in an affected family member.

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FHTL**

**HTLV I/II DNA, Qualitative Real-Time PCR**

**Reference Values:**
Reference Range: Not Detected

**FHAM**

**Human Anti-mouse Antibody (HAMA)**

**Reference Values:**
< or = 74 ng/mL

**HCG**

**Human Chorionic Gonadotropin (hCG) Immunostain, Technical Component Only**

**Clinical Information:** Human chorionic gonadotropin (hCG) is a heterodimeric hormone of 36 kD with subunits designated alpha and beta that is produced by the syncytiotrophoblasts of the placenta and has the same biologic properties as pituitary luteinizing hormone. HCG stimulates androgen and progesterone production in females and helps to maintain the corpus luteum of pregnancy. Many neoplasms including choriocarcinomas and adenocarcinomas may express HCG.

**Useful For:** Aids in the identification human chorionic gonadotropin expression in neoplasms.

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant
Human Chorionic Gonadotropin (hCG), Quantitative, Pregnancy, Serum

Clinical Information: Human chorionic gonadotropin (hCG) is a glycoprotein hormone that consists of 2 subunits (alpha and beta chains), which are associated to comprise the intact hormone. The alpha subunit is similar to those of luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone. The beta subunit of hCG differs from other pituitary glycoprotein hormones, which results in its unique biochemical and immunological properties. This method quantitates the sum of intact hCG plus the beta subunit. hCG is produced in the placenta during pregnancy. In nonpregnant individuals, it can also be produced by tumors of the trophoblast, germ cell tumors with trophoblastic components, and some nontrophoblastic tumors. The biological action of hCG serves to maintain the corpus luteum during pregnancy. It also influences steroid production. The serum in pregnant individuals contains mainly intact hCG. Measurement of the hCG concentration permits the diagnosis of pregnancy as early as 1 week after conception.

Useful For: Early detection of pregnancy Investigation of suspected ectopic pregnancy or other pregnancy-related complications Monitoring in vitro fertilization patients

Interpretation: Values in pregnancy should double every 2 to 3 days for the first 6 weeks. Elevated concentrations of human chorionic gonadotropin (hCG) measured in the first trimester of pregnancy are observed in normal pregnancy, but may serve as an indication of chorionic carcinoma, hydatiform mole, or multiple pregnancy. Decreasing hCG concentrations indicate threatened or missed abortion, recent termination of pregnancy, ectopic pregnancy, gestosis or intrauterine death. Both normal and ectopic pregnancies generally yield positive results of pregnancy tests. The comparison of quantitative hCG measurements with the results of transvaginal ultrasonography (TVUS) may aid in the diagnosis of ectopic pregnancy. When an embryo is first large enough for the gestation sac to be visible on TVUS, the patient generally will have hCG concentrations between 1,000 and 2,000 IU/L. (These are literature values. Definitive values for this method have not been established at this time.) If the hCG value is this high and no sac is visible in the uterus, ectopic pregnancy is suggested. Elevated values will also be seen with choriocarcinoma and hydatiform mole. Peri- and postmenopausal females may have detectable hCG concentrations (< or = to 14 IU/L) due to pituitary production of hCG. Serum follicle-stimulating hormone measurement may aid in ruling-out pregnancy in this population. Cutoffs of greater than 20 to 45 IU/L have been suggested and are method dependent.

Reference Values:
Negative: <5 IU/L


Human Epididymis Protein 4, Serum

Clinical Information: Human epididymis protein 4 (HE4) belongs to the family of whey acidic four-disulfide core proteins. Currently, the biologic function of HE4 is unknown. HE4 has been shown to be overexpressed in 93% of serous, 100% of endometrioid, and 50% of clear cell ovarian carcinomas. In a
study of 233 patients with a pelvic mass, including 67 with epithelial ovarian cancer, HE4 had a higher sensitivity for ovarian cancer detection than cancer antigen 125 (CA 125), 72.9% versus 43.3%, respectively, at a specificity of 95%. Researchers also found HE4 to be elevated in more than half of the ovarian cancer patients who did not have elevated CA 125 levels; therefore, the combination of markers provided slightly improved cancer diagnostic sensitivity for the detection of ovarian cancer. The main established application of HE4 is in post-therapy monitoring of ovarian cancer patients, who had elevated pretreatment levels. In this setting, it complements CA 125 measurement and facilitates follow-up of patients with little or no CA 125 pretreatment elevations. Certain histological types of ovarian cancer (mucinous or germ cell tumors) rarely express HE4, therefore the use of HE4 is not recommended for monitoring of patients with these types of ovarian cancer.

**Useful For:** An aid in monitoring patients with treated epithelial ovarian cancer for recurrence or progression

**Interpretation:** Increase in human epididymis protein 4 (HE4) suggests recurrence or disease progression, while a decrease suggests therapeutic response. A change in serum HE4 concentration of greater than or equal to 20% is considered significant.

**Reference Values:**
- Females: \(<\text{ or }\leq 140\text{ pmol/L}\)
- Males: Not applicable

**Clinical References:**

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**Human Herpes Virus, Type 8 (HHV-8) Immunostain, Technical Component Only**

**Clinical Information:** Human herpes virus type 8 (HHV-8) infection can lead to the development of lymphoproliferative diseases or other neoplasms, especially in the setting of HIV. These neoplasms include the plasma cell variant of Castleman disease, Kaposi sarcoma, and primary effusion lymphoma.

**Useful For:** Aids in the identification of human herpes virus type 8 infection

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
Human Herpesvirus 6 (HHV-6A and HHV-6B) by Quantitative PCR

**Reference Values:**
Not detected

The quantitative range of this assay is 3.0 – 6.0 log copies/mL (1,000 - 999,000 copies/mL).

A negative result (less than 3.0 log copies/mL or less than 1,000 copies/mL) does not rule out the presence of PCR inhibitors in the patient specimen or HHV6 DNA in concentrations below the level of detection of the test. Inhibition may also lead to underestimation of viral quantitation.

**Clinical Information:**
Human herpesvirus-6 (HHV-6) is a member of the Herpesviridae family. These viruses contain DNA surrounded by a lipid envelope. Among members of this group, this virus is most closely related to cytomegalovirus (CMV) and HHV-7. As with other members of the herpesvirus group (herpes simplex virus [HSV] 1, HSV 2, varicella zoster virus [VZV], CMV, Epstein-Barr virus [EBV], HHV-7, HHV-8), HHV-6 may cause primary and reactivated infections subsequent to latent association with cells.(1) Infection with HHV-6 occurs early in childhood. Most adults (80%-90%) have been infected with this virus. HHV-6 was first linked with exanthem subitum (roseola infantum) in 1998; since then, the virus has been associated with central nervous system disease almost exclusively in immunocompromised patients.(1) HHV-6 is commonly detected in patients posttransplantation. Clinical symptoms associated with this viral infection include febrile illness, pneumonitis, hepatitis, encephalitis, and bone marrow suppression. However, the majority of HHV-6 infections are asymptomatic.(2) The incidence of HHV-7 infection and its clinical manifestations posttransplantation are less well characterized. HHV-6 is designated as variant A (HHV-6A) or variant B (HHV-6B) depending on restriction enzyme digestion patterns and on its reaction with monoclonal antibodies. Generally, variant B has been associated with exanthem subitum, whereas variant A has been found in many immunosuppressed patients.(3)

**Useful For:** As an adjunct in the rapid diagnosis of human herpesvirus-6 infection in plasma specimens

**Interpretation:**
A positive result indicates the presence of specific DNA from human herpesvirus-6 (HHV-6) and supports the diagnosis of infection with this virus. A negative result indicates the absence of detectable DNA from HHV-6 in the specimen, but it does not negate the presence of the virus or active or recent disease.

**Reference Values:**
Negative

**Clinical References:**

Human Herpesvirus-6, Molecular Detection, PCR, Spinal Fluid

**Clinical Information:**
Human herpesvirus-6 (HHV-6) is a member of the Herpesviridae family. These viruses contain DNA surrounded by a lipid envelope. Among members of this group, this virus is most closely related to cytomegalovirus (CMV) and HHV-7. As with other members of the herpesvirus group (herpes simplex virus [HSV] 1, HSV 2, varicella zoster virus, CMV, Epstein-Barr virus, HHV-7, HHV-8), HHV-6 may cause primary and reactivated infections subsequent to latent association with cells.(1) Infection with HHV-6 occurs early in childhood. Most adults (80%-90%) have been infected with this virus. HHV-6 was first linked with exanthem subitum (roseola infantum) in 1998; since then, the
virus has been associated with central nervous system disease almost exclusively in immunocompromised patients.(1) HHV-6 is commonly detected in patients posttransplantation. Clinical symptoms associated with this viral infection include febrile illness, pneumonitis, hepatitis, encephalitis, and bone marrow suppression. However, the majority of HHV-6 infections are asymptomatic.(2) The incidence of HHV-7 infection and its clinical manifestations posttransplantation are less well characterized. HHV-6 is designated as variant A (HHV-6A) or variant B (HH6-B) depending on restriction enzyme digestion patterns and on its reaction with monoclonal antibodies. Generally, variant B has been associated with exanthem subitum, whereas variant A has been found in many immunosuppressed patients.(3)

**Useful For:** As an adjunct in the rapid diagnosis of human herpesvirus-6 infection in cerebrospinal fluid specimens

**Reference Values:**
Negative


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**FHMPV**

**Human Metapneumovirus (hMPV) RNA**

**Reference Values:**
Reference Range: Not Detected

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**HPVP**

**Human Papillomavirus (HPV) DNA Detection with Genotyping, High Risk Types by PCR with Papanicolaou Smear Reflex, ThinPrep**

**Clinical Information:** Persistent infection with human papillomavirus (HPV) is the principal cause of cervical cancer and its precursor cervical intraepithelial neoplasia (CIN).(1-3) The presence of HPV has been implicated in >99% of cervical cancers worldwide. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8,000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPVs that can infect the human anogenital mucosa. However, data suggest that 14 of these types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high risk (HR) for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic, and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers.(1-3) Although persistent infection with HR-HPV is necessary for the development of cervical cancer and its precursor lesions, only a very small percentage of infections progress to these disease states. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. An infection with any HPV type can produce CIN although this also usually resolves once the HPV infection has been cleared. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to detect early precursors to cervical cancer. Although it has decreased the death rates due to cervical cancer dramatically in those countries, the Pap smear and subsequent liquid based cytology methods require subjective interpretation by highly trained cytopathologists and misinterpretation can occur. Cytological abnormalities are primarily due to infection with HPV; however, various inflammatory conditions or sampling variations can result in false-positive cytology results. Triage of an abnormal cytology result may involve repeat testing, colposcopy, and biopsy. A histologically confirmed high-grade lesion must be surgically removed or ablated in order to prevent the development of invasive cervical cancer.
Nucleic acid (DNA) testing by PCR has become a standard noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may 1) increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology and 2) reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance (ASC-US). Data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 and/or HPV-18 positive women is 11.4% (95% confidence interval [CI] 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for “other” HR-HPV genotypes and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV negative women.(4) Based in part on these data, the American Society for Colposcopy and Cervical Pathology (ASCCP) now recommends that HPV 16/18 genotyping be performed on women who are positive for HR-HPV, but negative by routine cytology. Women who are found to be positive for HPV-16 and/or -18 may be referred to colposcopy, while women who are negative for genotypes 16 and/or 18 may have repeat cytology and HR-HPV testing in 12 months.(1) Recently, the Food and Drug Administration (FDA) approved the use of the Roche Cobas HPV test for primary screening of cervical and endocervical samples collected in ThinPrep/PreservCyt media. In addition, the age at which patients may be screened by the HPV test dropped from 30 to 25 years old.

**Useful For:** Screening for infection with high-risk (HR) human papillomavirus associated with the development of cervical cancer Individual genotyping of HPV-16 and/or HPV-18, if present

**Interpretation:** HPV with Genotyping PCR: A positive result indicates the presence of human papillomavirus (HPV) DNA due to 1 or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous cells of undetermined significance (ASC-US) Pap smear result and who are positive for high-risk (HR)-HPV, consider referral for colposcopy, if clinically indicated. For women aged 25 years and older who are positive for HPV-16 and/or HPV-18, but negative by Pap smear, consider referral for colposcopy, if clinically indicated. Cytology: Standard reporting, as defined by the Bethesda System (TBS) is utilized.

**Reference Values:**
HPV with Genotyping PCR: Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
ThinPrep Pap Test: Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.

**Clinical References:**
High-Risk Types by PCR, SurePath

Useful For: Detection of high-risk (HR) genotypes associated with the development of cervical cancer An aid in triaging women with abnormal Pap smear results Individual genotyping of human papillomavirus (HPV)-16 and/or HPV-18, if present

Interpretation: A positive result indicates the presence of human papillomavirus (HPV) DNA due to 1 or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous cells of undetermined significance (ASC-US) Pap smear result and who are positive for high-risk (HR) HPV, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear result but who are positive for HPV-16 and/or HPV-18, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear, positive HR HPV test result, but who are negative for HPV-16 and HPV-18, consider repeat testing by both cytology and a HR HPV test in 12 months.

Reference Values:
Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68

Clinical References:

Human Papillomavirus (HPV) DNA Detection with Genotyping, High-Risk Types by PCR, ThinPrep

Clinical Information: Persistent infection with human papillomavirus (HPV) is the principal cause of cervical cancer and its precursor cervical intraepithelial neoplasia (CIN).(1-3) The presence of HPV has been implicated in more than 99% of cervical cancers worldwide. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8,000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPVs that can infect the human anogenital mucosa. However, data suggest that 14 of these types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high risk (HR) for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers.(1-3) Although persistent infection with HR HPV is necessary for the development of cervical cancer and its precursor lesions, only a very small percentage of infections progress to these disease states. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. An infection with any HPV type can produce CIN, although this also usually resolves once the HPV infection has been cleared. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to detect early precursors to cervical cancer. Although it has decreased the death rates due to cervical cancer dramatically in those countries, the Pap smear and subsequent liquid-based cytology methods require subjective interpretation by highly trained cytopathologists and misinterpretation can occur. Cytological abnormalities are primarily due to infection with HPV; however, various inflammatory conditions or
sampling variations can result in false-positive cytology results. Triage of an abnormal cytology result may involve repeat testing, colposcopy, and biopsy. A histologically confirmed high-grade lesion must be surgically removed or ablated in order to prevent the development of invasive cervical cancer. Nucleic acid (DNA) testing by PCR has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may 1) increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology and 2) reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance (ASC-US). Recently, data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 and/or HPV-18 positive women is 11.4% (95% confidence interval [CI] 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for other HR-HPV genotypes, and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV-negative women.(4) Based in part on these data, the American Society for Colposcopy and Cervical Pathology (ASCCP) now recommends that HPV 16/18 genotyping be performed on women who are positive for HR-HPV but negative by routine cytology. Women who are found to be positive for HPV-16 and/or -18 may be referred to colposcopy, while women who are negative for genotypes 16 and 18 may have repeat cytology and HR-HPV testing in 12 months.(1)

Useful For: Detection of high-risk (HR) genotypes associated with the development of cervical cancer Aids in triaging women with abnormal Pap smear results Individual genotyping of human papillomavirus (HPV)-16 and/or HPV-18, if present Results of HPV-16 and HPV-18 genotyping can aid in triaging women with positive HR-HPV but negative Pap smear results

Interpretation: A positive result indicates the presence of human papillomavirus (HPV) DNA due to 1 or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous cells of undetermined significance (ASC-US) Pap smear result and who are positive for high-risk (HR) HPV, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear result but who are positive for HPV-16 and/or HPV-18, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear, positive-HR-HPV test result, but who are negative for HPV-16 and HPV-18, consider repeat testing by both cytology and a HR-HPV test in 12 months.

Reference Values:
Negative for human papillomavirus (HPV) genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

Clinical References:

Human Papillomavirus (HPV) High-Risk E6/E7, RNA In Situ Hybridization

Clinical Information: This assay is intended to identify the presence of human papillomavirus (HPV) E6/E7 transcripts from high-risk genotypes. This test has been shown to be more sensitive than HPV DNA in situ hybridization (ISH). Patients with HPV-related oropharyngeal squamous cell carcinoma (OPSCC) have shown better disease-specific survival and overall survival when compared to HPV-negative cases of OPSCC. An indication for this test is p16 expression by immunohistochemistry and negative HPV DNA ISH. In this instance, consideration should be given to the possibility of a
false-negative HPV DNA ISH result.

**Useful For:** Stratification of oropharyngeal squamous cell carcinoma

**Interpretation:** This test, when not accompanied by a pathology consultation request, will be answered as either positive or negative. If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test.

**Reference Values:**
Results are reported as positive or negative for types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82.

**Clinical References:**

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**HPVHL**

**Human Papillomavirus (HPV) High/Low Risk, DNA In Situ Hybridization**

**Clinical Information:** Human papillomavirus (HPV) infections with low-risk genotypes (6, 11) can cause benign hyperplasia such as condylomas and papillomas. Persistent infections with high-risk genotypes (16, 18, 31, 33, and 51) are associated with cervical, vaginal, vulvar, and head and neck malignancies. Patients with HPV-related oropharyngeal squamous cell carcinoma (OPSCC) have shown better disease-specific survival and overall survival when compared to HPV-negative cases of OPSCC.

**Interpretation:** This test, when not accompanied by a pathology consultation request, will be answered as either positive or negative. If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test.

**Reference Values:**
Results are reported as positive or negative for types 6 and 11 (low risk), and 16, 18, 31, 33, 51 (high risk).

**Clinical References:**

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**HPVLR**

**Human Papillomavirus (HPV) Low Risk, DNA In Situ Hybridization**

**Clinical Information:** Human papillomavirus infections with low-risk genotypes (6, 11) can cause benign hyperplasia such as condylomas and papillomas.

**Useful For:** Detection of human papillomavirus (HPV) DNA from low-risk genotypes (6, 11)

**Interpretation:** This test, when not accompanied by a pathology consultation request, will be answered as either positive or negative. If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test.
Reference Values:
Results are reported as positive or negative for types 6 and 11.


HPVHR 70463 Human Papillomavirus (HPV), High-Risk, DNA In Situ Hybridization

Clinical Information: Persistent infections with high-risk human papillomavirus (HPV) genotypes (16, 18, 31, 33, and 51) are associated with cervical, vaginal, vulvar, and head and neck malignancies. Patients with HPV-related oropharyngeal squamous cell carcinoma (OPSCC) have shown better disease-specific survival and overall survival when compared to HPV-negative cases of OPSCC.

Useful For: Detection of human papillomavirus DNA from high-risk genotypes (16, 18, 31, 33, and 51)

Interpretation: This test, when not accompanied by a pathology consultation request, will be answered as either positive or negative. If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test.


FHPL 91178 Human Placental Lactogen (HPL)

Reference Values:
Males and nonpregnant Woman: 0.00 - 0.10 mcg/mL
1st Trimester of Pregnancy: 0.20 - 2.10 mcg/mL
2nd Trimester of Pregnancy: 0.50 - 6.70 mcg/mL
3rd Trimester of Pregnancy: 4.50 - 12.80 mcg/mL

HPL 70462 Human Placental Lactogen (HPL) Immunostain, Technical Component Only

Clinical Information: Human placental lactogen (HPL) is a hormone secreted by the placenta during normal pregnancy. Detection of this hormone may help in diagnosis of placenta-related tumors such as trophoblastic tumors and choriocarcinomas.

Useful For: Aids in the identification of placenta-related tumors

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be
performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Human T-Cell Lymphotropic Virus Types I and II (HTLV-I/-II) Antibody Confirmation, Serum

Clinical Information: Human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II) are closely related exogenous human retroviruses. HTLV-I was first isolated in 1980 from a patient with a cutaneous T-cell lymphoma, while HTLV-II was identified from a patient with hairy cell leukemia in 1982. HTLV-I infection is endemic in southwestern Japan, Caribbean basin, Melanesia, and parts of Africa, where HTLV-I seroprevalence rates are as high as 15% in the general population. In the United States, the combined HTLV-I and HTLV-II seroprevalence rate is about 0.016% among voluntary blood donors. About half of these infected blood donors are infected with HTLV-I, with most of them reporting a history of birth in HTLV-I-endemic countries or sexual contact with persons from the Caribbean or Japan. Smaller percentages report a history of either injection drug use or blood transfusion. Transmission of HTLV-I occurs from mother to fetus, sexual contact, blood transfusion, and sharing of contaminated needles. Two diseases are known to be caused by HTLV-I infection, adult T-cell leukemia or lymphoma (ATL), and a chronic degenerative neurologic disease known as HTLV-I-associated myelopathy (HAM) or tropical spastic paraparesis (TSP). Cases of polymyositis, chronic arthropathy, panbronchiolitis, and uveitis also have been reported in HTLV-I-infected patients. HTLV-II is prevalent among injection drug users in the United States and in Europe, and more than 80% of HTLV infections in drug users in the United States are due to HTLV-II. HTLV-II also appears to be endemic in Native American populations, including the Guaymi Indians in Panama and Native Americans in Florida and New Mexico. HTLV-II-infected blood donors most often report either a history of injection drug use or a history of sexual contact with an injection drug user. A smaller percentage of infected individuals report a history of blood transfusion. HTLV-II is transmitted similarly to HTLV-I, but much less is known about the specific modes and efficiency of transmission of HTLV-II. The virus can be transmitted by transfusion of cellular blood products (whole blood, red blood cells, and platelets). HTLV-II infection has been associated with hairy-cell leukemia, but definitive evidence is lacking on a viral etiologic role. HTLV-II has also been linked with neurodegenerative disorders characterized by spastic paraparesis and variable degrees of ataxia. Infection by these viruses results in the appearance of specific antibodies against the viruses that can be detected by serologic tests such as EIA. For accurate diagnosis of HTLV-I or HTLV-II infection, all initial screening test-reactive results should be verified by a confirmatory test, such as Western blot or line immunoassay.

Useful For: Confirmatory detection of human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II)-specific IgG antibodies in human serum specimens that are consistently reactive by initial screening tests. Differentiating between HTLV-I- and HTLV-II-specific IgG antibodies

Interpretation: Negative confirmatory test results indicate the absence of both human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II)-specific IgG antibodies in serum. A reactive screening (EIA) result with a negative or indeterminate confirmatory (line immunoassay) test result suggests either a false-reactive screening test result or a seroconverting HTLV infection. Repeat testing in 1 to 2 months can clarify the final infection status. Persistently indeterminate confirmatory test results indicate absence of HTLV infection. Positive results for HTLV-I antibodies indicate the confirmed
presence of HTLV-I IgG antibodies in serum, based on 2 visible antibody bands that include gp21-I/-II band, or 3 or more bands, and the sum of the gp46-I and p19-I band intensity is greater than the gp46-II band intensity. Positive results for HTLV-II antibodies indicate the confirmed presence of HTLV-II IgG antibodies in serum, based on 2 visible antibody bands that include gp21-I/-II band, or 3 or more bands, and the gp46-II band intensity is a) greater than the gp46-I band intensity and b) equal or greater than the sum of the gp46-I and p19-I band intensity. Indeterminate results indicate the presence of gp21-I/-II band only or combination of any 2 bands without a detectable gp21-I/-II band. Patients with indeterminate test results with known risk factors for HTLV-I or HTLV-II infection should undergo repeat confirmatory antibody testing in 1 to 2 months to determine final infection status. Differentiation of HTLV-I and HTLV-II infection is not possible (ie, nontypeable HTLV antibodies) when the band intensity pattern does not meet the criteria of positive HTLV-I or HTLV-II antibody band intensity pattern.

Reference Values:
Negative
This confirmatory assay should be ordered only on specimens that are reactive by an anti-HTLV-I/-II screening immunoassay.

Clinical References:

### Human T-Cell Lymphotropic Virus Types I and II (HTLV-I/-II)

#### Antibody Screen with Confirmation, Serum

**Clinical Information:** Human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II) are closely related exogenous human retroviruses. HTLV-I was first isolated in 1980 from a patient with a cutaneous T-cell lymphoma, while HTLV-II was identified from a patient with hairy cell leukemia in 1982. HTLV-I infection is endemic in southwestern Japan, Caribbean basin, Melanesia, and parts of Africa, where HTLV-I seroprevalence rates are as high as 15% in the general population. In the United States, the combined HTLV-I and HTLV-II seroprevalence rate is about 0.016% among voluntary blood donors. About half of these infected blood donors are infected with HTLV-I, with most of them reporting a history of birth in HTLV-I-endemic countries or sexual contact with persons from the Caribbean or Japan. Smaller percentages report a history of either injection drug use or blood transfusion. Transmission of HTLV-I occurs from mother to fetus, sexual contact, blood transfusion, and sharing of contaminated needles. Two diseases are known to be caused by HTLV-I infection: adult T-cell leukemia or lymphoma, and a chronic degenerative neurologic disease known as HTLV-I-associated myelopathy or tropical spastic paraparesis. Cases of polymyositis, chronic arthropathy, panbronchiolitis, and uveitis also have been reported in HTLV-I-infected patients. HTLV-II is prevalent among injection drug users in the United States and in Europe, and >80% of HTLV infections in drug users in the United States are due to HTLV-II. HTLV-II also appears to be endemic in Native American populations, including the Guaymi Indians in Panama and Native Americans in Florida and New Mexico. HTLV-II-infected blood donors most often report either a history of injection drug use or a history of sexual contact with an injection drug user. A smaller percentage of infected individuals report a history of blood transfusion. HTLV-II is transmitted similarly to HTLV-I, but much less is known about the specific modes and efficiency of transmission of HTLV-II. The virus can be transmitted by transfusion of cellular blood products (whole blood, red blood cells, and platelets). HTLV-II infection has been associated with hairy-cell leukemia, but definitive evidence is lacking on a viral etiologic role. HTLV-II has also been linked with neurodegenerative disorders characterized by spastic paraparesis and variable degrees of ataxia. Infection by these viruses results in the appearance of specific antibodies against the viruses that can be detected by serologic tests such as EIA. For accurate diagnosis of HTLV-I or HTLV-II infection, all initially screening test-reactive results should be verified by a confirmatory test, such as Western blot or line
Useful For: Qualitative detection of human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II)-specific antibodies with confirmation and differentiation between HTLV-I and HTLV-II infection

Interpretation: Negative screening results indicate the absence of both human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II)-specific IgG antibodies in serum. A reactive screening test result is suggestive of infection with either HTLV-I or HTLV-II. However, this result does not confirm infection (eg, low specificity), and it cannot differentiate between HTLV-I and HTLV-II infection. Specimens with reactive screening test results will be tested automatically by the line immunoassay (LIA) confirmatory test. Positive LIA results provide confirmatory evidence of infection with HTLV-I or HTLV-II. A reactive screening result with a negative or indeterminate confirmatory test result suggests either a false-reactive screening test result or a seroconverting HTLV infection. Repeat testing in 1 to 2 months can clarify the final infection status. Persistently indeterminate confirmatory test results indicate absence of HTLV infection.

Reference Values:
Negative


Hunter Syndrome, Full Gene Analysis

Clinical Information: Mucopolysaccharidosis type II (MPS-II), also known as Hunter syndrome, is a rare X-linked condition caused by mutations in the IDS gene. MPS-II is characterized by reduced or absent activity of the iduronate 2-sulfatase enzyme. The clinical features and severity of symptoms of MPS-II are widely variable, ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, joint contractures, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. Female carriers are usually asymptomatic. The IDS gene is located on the X chromosome and has 9 exons. IDS is the only known gene to be associated with MPS-II. The recommended first-tier test for MPS-II is biochemical testing that measures iduronate 2-sulfatase enzyme activity in fibroblasts: IDNS / Iduronate Sulfatase, Fibroblasts. Individuals with decreased or absent enzyme activity are more likely to have a mutation in the IDS gene identifiable by molecular gene testing. However, enzymatic testing is not reliable to detect carriers. This test screens for mutations in all 9 exons of the IDS gene.

Useful For: Confirmation of a diagnosis of mucopolysaccharidosis type II (Hunter syndrome) Carrier testing when there is a family history of mucopolysaccharidosis type II (Hunter syndrome), but disease-causing mutations have not been previously identified

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


Huntington Disease, Molecular Analysis

Clinical Information: Huntington disease (HD) is an autosomal dominant progressive neurodegenerative disorder caused by a CAG repeat expansion in the HTT gene. HD is associated with cognitive impairment leading to dementia and a wide range of neuropsychiatric problems including apathy, depression, anxiety, and other behavioral disturbances. Additionally, affected individuals typically develop extrapyramidal symptoms (eg, dystonia, dysarthria, chorea, gait disturbance, postural instability, oculomotor dysfunction).

Useful For: Molecular confirmation of clinically suspected cases of Huntington disease (HD) Presymptomatic testing for individuals with a family history of HD and a documented expansion in the HTT gene

Interpretation: An interpretive report will be provided.

Reference Values:
Normal alleles: <27 CAG repeats
Intermediate alleles: 27-35 CAG repeats
Reduced penetrance: 36-39 CAG repeats
Full penetrance: >39 CAG repeats
An interpretive report will be provided.


MPS1Z Hurler Syndrome, Full Gene Analysis

Clinical Information: Mucopolysaccharidosis type I (MPS-I) can be categorized into 3 syndromes, Hurler syndrome, Scheie syndrome, and Hurler-Scheie syndrome. MPS-I, inherited in an autosomal recessive manner, is caused by mutations in the IDUA gene. Furthermore, MPS-I is characterized by reduced or absent activity of the alpha-L-iduronidase enzyme. Hurler syndrome (severe MPS-I) has early onset and consists of skeletal deformities, coarse facial features, corneal clouding, hepatosplenomegaly, cardiac involvement, hearing loss, and respiratory tract infections. Developmental delay is noticed as early as 12 months with death occurring usually before 10 years of age. Hurler-Scheie syndrome and Scheie syndrome (attenuated MPS-I) have onset between 3 to 10 years of age and consist of corneal clouding, cardiac involvement, moderate-to-severe hearing loss, and progressive pulmonary disease. Typically skeletal and joint involvement is the most significant source of discomfort for attenuated MPS-I. Intellect with attenuated MPS-I is typically normal or nearly normal. The IDUA gene is located on chromosome 4 and has 14 exons. IDUA is the only known gene to be associated with MPS-I, and the 3 syndromes appear to be caused by different combinations of mutations. The recommended first-tier test for MPS-I is biochemical testing that measures alpha-L-iduronidase enzyme activity in blood or fibroblasts: IDSWB / Alpha-L-Iduronidase, Blood or IDST / Alpha-L-Iduronidase, Fibroblasts. Individuals with decreased or absent enzyme activity are more likely to have 2 identifiable mutations in the IDUA gene by molecular genetic testing. However, enzymatic testing is not reliable to detect carriers.

Useful For: Identifying mutations within the IDUA gene Confirmation of a diagnosis of mucopolysaccharidosis type I (MPS-I) Carrier testing when there is a family history of MPS- I, but disease-causing mutations have not been previously identified
**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**FHMTB 58081**

Hydrocodone and metabolites

**Reference Values:**

**Reference Range:**

- Hydrocodone, unconjugated: 10 - 100 ng/mL
- Hydromorphone, unconjugated: 1 - 30 ng/mL
- Dihydrocodeine, unconjugated: Not established ng/mL

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**HYDCU 62614**

Hydrocodone with Metabolite Confirmation, Urine

**Clinical Information:** Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation, and 6-keto reduction to the 6-beta hydroxymetabolites. Hydromorphone and norhydrocodone are both metabolites of hydrocodone. Dihydrocodeine is also a minor metabolite. Trace amounts of hydrocodone can also be found in the presence of approximately 100-fold higher concentrations of oxycodone or hydromorphone since it can be a pharmaceutical impurity in these medications. The presence of hydrocodone >100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is metabolized primarily in the liver and is excreted primarily as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6-hydroxy reduction metabolites. The presence of hydromorphone >100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is also a metabolite of hydrocodone; therefore, the presence of hydromorphone could also indicate exposure to hydrocodone. The detection interval for the opiates is generally 2 to 3 days after last ingestion.

**Useful For:** Detection and quantification of hydrocodone, norhydrocodone, and hydromorphone in urine

**Interpretation:** This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

**Reference Values:**

- Negative
- Cutoff concentrations:
  - Hydrocodone-by LC-MS/MS: 25 ng/mL
  - Norhydrocodone-by LC-MS/MS: 25 ng/mL
  - Hydromorphone-by LC-MS/MS: 25 ng/mL

**Hydromorphone Confirmation, Urine**

**Clinical Information:** Opiates are the natural or synthetic drugs that have a morphine-like pharmacological action. Medically, opiates are used primarily for relief of pain. Opiates include morphine and drugs structurally similar to morphine (eg, codeine, hydrocodone, hydromorphone, oxycodone). Hydromorphone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation, and 6-keto reduction to the 6-beta hydroxymetabolites. Hydromorphone is a metabolite of hydrocodone. The presence of hydrocodone >100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is metabolized primarily in the liver and is excreted primarily as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6-hydroxy reduction metabolites. The presence of hydromorphone >100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is also a metabolite of hydrocodone; therefore, the presence of hydromorphone could also indicate exposure to hydrocodone.

**Useful For:** Detection and quantification of hydromorphone in urine

**Interpretation:** This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

**Reference Values:**

Negative

Cutoff concentrations:

Hydromorphone-by LC-MS/MS: 25 ng/mL


**Hydroxychloroquine, Serum**

**Clinical Information:** Hydroxychloroquine is an antimalarial drug used to treat or prevent malaria. It is highly effective against erythrocytic forms of Plasmodium, but not effective against exoerythrocytic forms of parasites. Hydroxychloroquine is also used to treat symptoms of acute or chronic rheumatoid arthritis and lupus erythematosus. Adult doses range from 400 mg/week for suppressive therapy to 1,200 mg/day for acute malaria attacks. Typical daily doses of 200 to 600 mg are used for lupus and rheumatoid diseases. Hydroxychloroquine has a long terminal elimination half-life in blood (>40 days), which exceed those in plasma. The oral bioavailability averages 79%. Hydroxychloroquine accumulates in several organs, especially melanin-containing retina and skin. Mild to moderate overdose can result in gastrointestinal effects (ie, nausea, vomiting, and abdominal pain), headache, visual and hearing disturbances, and neuromuscular excitability. Acute hepatitis, cardiotoxicity, and retinopathy may occur with therapeutic doses. The effects of overdosage with hydroxychloroquine include headache, drowsiness, visual disturbances, convulsions, cardiovascular collapse, and respiratory arrest. Toxic retinopathy has also been associated with higher doses and longer duration of use.

**Useful For:** Monitoring serum hydroxychloroquine concentrations, assessing compliance, and adjusting dosage in patients
**Interpretation:** The serum concentration should be interpreted in the context of the patient's clinical response and may provide useful information in patients showing poor response, noncompliance, or adverse effects.

**Reference Values:**
For suppressive treatment of malaria, suggested plasma or serum concentrations should be >10 ng/mL.

For systemic lupus erythematosus, proposed blood target concentrations should be 1,000 ng/mL.

**Clinical References:**

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**Hydroxycorticosterone, 18**

**Reference Values:**

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<td>10-670</td>
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</tr>
<tr>
<td>Full Term Day 3</td>
<td>31-546</td>
</tr>
<tr>
<td>31 Days-11 Months</td>
<td>5-220</td>
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<td>12-23 Months</td>
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<td>10-14 Years</td>
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<tr>
<td>Adults</td>
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<tr>
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<tr>
<td>Adults 8:00 AM Upright</td>
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**Clinical Information:** Acylcarnitine analysis is included in newborn screening blood testing and is utilized for detection of several inborn errors of metabolism, including fatty acid oxidation disorders (FAOD) and organic acidemias (OA). A limitation of this analytic method is its inability to differentiate between several isomers. Additional testing of 2-hydroxy glutaric acid (2OH-GA), 3-hydroxy glutaric acid (3OH-GA), glutaric acid (GA), methylsuccinic acid (MSA), and ethylmalonic acid (EMA) by LC-MS/MS allows better differentiation among C4-acylcarnitine and glutarylcarbnitine/C10-OH isomers. C4-acylcarnitine represents both butyrylcarnitine and isobutyrylcarnitine and is elevated in short-chain acyl Co-A dehydrogenase (SCAD) deficiency, isobutyryl-CoA dehydrogenase (IBDH) deficiency, and ethylmalonic encephalopathy (EE). SCAD deficiency is a condition affecting fatty acid metabolism, with reported symptoms of hypoglycemia, lethargy, developmental delays, and failure to thrive. There is controversy on whether a biochemical diagnosis necessarily confers clinical symptoms. IBDH deficiency is characterized by cardiomyopathy, hypotonia, and developmental delays, although many individuals with IBDH deficiency are asymptomatic. EE is a rare progressive encephalopathy associated with hypotonia, seizures, and abnormal movements. Individuals with SCAD deficiency demonstrate elevated plasma EMA and MSA levels and individuals with EE show only elevations in EMA, while individuals with IBDH deficiency do not typically have elevations in either EMA or MSA. Glutarylcarbnitine (C5-DC) is elevated in glutaric acidemia type 1 (GA-1), but is not differentiated from C10-OH acylcarnitine. GA-1, is caused by a deficiency of glutaryl-CoA dehydrogenase and is characterized by bilateral striatal brain injury leading to dystonia, often a result of acute neurologic crises triggered by illness. Individuals with GA-1 typically show elevations of glutaric acid and 3OH-GA, even in those considered to be “low excretors.” Glutaric acidemia (GA-2), also known as multiple acyl-CoA dehydrogenase deficiency (MADD), is caused by defects in either the electron transfer flavoprotein (ETF) or ETF-ubiquinone oxidoreductase. This disease can be severe and is often fatal in the first weeks of life, with typical symptoms of hypoglycemia, muscle weakness, metabolic acidosis, dysmorphic features, cardiac defects or arrhythmias, renal cysts, and fatty infiltration of the liver. GA-2 can have a milder presentation, also known as ethylmalonic-adipic aciduria, with Reye-like illnesses in childhood and muscle weakness in childhood and adulthood. In addition to elevations in glutaric acid, individuals with GA-2 can also show increased EMA, MSA, and 2OH-GA. The American College of Medical Genetics (ACMG) newborn screening work group published diagnostic algorithms for the follow-up of infants who had a positive newborn screening result. For more information, see www.acmg.net.

**Useful For:** Evaluation of patients with an abnormal newborn screen showing elevations of glutarylcarbnitine (C5-DC) Evaluation of patients with abnormal newborn screens showing elevations of C4-acylcarnitine to aid in the differential diagnosis of short-chain acyl-CoA dehydrogenase and isobutyryl-CoA dehydrogenase deficiencies Diagnosis of glutaric acidemia type 1 Aids in diagnosis of glutaric acidemia type 2

**Interpretation:** Elevations of ethylmalonic acid (EMA) and methylsuccinic acid (MSA) are consistent with a diagnosis of short-chain acyl Co-A dehydrogenase (SCAD) deficiency. Elevation of EMA is consistent with a diagnosis of ethylmalonic encephalopathy. Normal levels of EMA in the context of elevated C4 is consistent with a diagnosis of isobutyryl-CoA dehydrogenase (IBDH) deficiency. Elevation of glutaric acid (GA) and 3-hydroxy glutaric acid (3OH-GA) are consistent with a diagnosis of glutaric acidemia type 1 (GA-1). Elevation of GA, 2-hydroxy glutaric acid (2OH-GA), 3OH-GA, EMA, and MSA are consistent with a diagnosis of glutaric acidemia (GA-2).

**Reference Values:**
- 2-OH Glutaric acid: < or =25 nmol/mL
- 3-OH Glutaric acid: < or =1.5 nmol/mL
- Glutaric acid: < or =1.5 nmol/mL
Methylsuccinic acid: < or = 0.45 nmol/mL
Ethylmalonic acid: < or = 3.5 nmol/mL

Clinical References:

Hydroxyglutaric Acids, Glutaric Acid, Ethylmalonic Acid, and Methylsuccinic Acid, Plasma

Clinical Information: Acylcarnitine analysis is included in newborn screening blood testing and is utilized for detection of several inborn errors of metabolism, including fatty acid oxidation disorders (FAOD) and organic acidemias (OA). A limitation of this analytic method is its inability to differentiate between several isomers. Additional testing of 2-hydroxy glutaric acid (2OH-GA), 3-hydroxy glutaric acid (3OH-GA), glutaric acid (GA), methylsuccinic acid (MSA), and ethylmalonic acid (EMA) by LC-MS/MS allows better differentiation among C4 acylcarnitine and glutarylcarnitine/C10-OH isomers. C4 acylcarnitine represents both butyrylcarnitine and isobutyrylcarnitine and is elevated in short chain acyl Co-A dehydrogenase (SCAD) deficiency, isobutyryl-CoA dehydrogenase (IBDH) deficiency, and ethylmalonic encephalopathy (EE). SCAD deficiency is a condition affecting fatty acid metabolism, with reported symptoms of hypoglycemia, lethargy, developmental delays, and failure to thrive. There is controversy on whether a biochemical diagnosis necessarily confers clinical symptoms. IBDH deficiency is characterized by cardiomyopathy, hypotonia, and developmental delays, although many individuals with IBDH deficiency are asymptomatic. EE is a rare progressive encephalopathy associated with hypotonia, seizures, and abnormal movements. Individuals with SCAD deficiency demonstrate elevated plasma EMA and MSA levels and individuals with EE show only elevations in EMA, while individuals with IBDH deficiency do not typically have elevations in either EMA or MSA. Glutarylcarnitine (C5-DC) is elevated in glutaric acidemia type 1 (GA-1), but is not differentiated from C10-OH acylcarnitine. GA-1 is caused by a deficiency of glutaryl-CoA dehydrogenase and is characterized by bilateral striatal brain injury leading to dystonia, often a result of acute neurologic crises triggered by illness. Individuals with GA-1 typically show elevations of glutaric acid and 3OH-GA, even in those considered to be "low excretors." Glutaric acidemia (GA-2), also known as multiple acyl-CoA dehydrogenase deficiency (MADD), is caused by defects in either the electron transfer flavoprotein (ETF) or ETF-ubiquinone oxidoreductase. This disease can be severe and is often fatal in the first weeks of life, with typical symptoms of hypoglycemia, muscle weakness, metabolic acidosis, dysmorphic features, cardiac defects or arrhythmias, renal cysts, and fatty infiltration of the liver. GA-2 can have a milder presentation, also known as ethylmalonic-adipic aciduria, with Reye-like illnesses in childhood and muscle weakness in childhood and adulthood. In addition to elevations in glutaric acid, individuals with GA-2 can also show increased EMA, MSA, and 2OH-GA. The American College of Medical Genetics (ACMG) newborn screening work group published diagnostic algorithms for the follow-up of infants who had a positive newborn screening result. For more information, see www.acmg.net.

Useful For: Evaluation of patients with an abnormal newborn screen showing elevations of glutarylcarnitine (C5-DC) Evaluation of patients with abnormal newborn screens showing elevations of C4- acylcarnitine to aid in the differential diagnosis of short chain acyl-CoA dehydrogenase and isobutyryl-CoA dehydrogenase deficiencies Diagnosis of glutaric acidemia type 1 Aids in diagnosis of glutaric acidemia type 2

Interpretation: Elevations of ethylmalonic acid (EMA) and methylsuccinic acid (MSA) are consistent with a diagnosis of short chain acyl Co-A dehydrogenase (SCAD) deficiency. Elevation of EMA is consistent with a diagnosis of ethylmalonic encephalopathy. Normal levels of EMA in the context of elevated C4 is consistent with a diagnosis of isobutyryl-CoA dehydrogenase (IBDH) deficiency. Elevation of glutaric acid (GA) and 3-hydroxy glutaric acid (3OH-GA) are consistent with a
diagnosis of glutaric acidemia type 1 (GA-1). Elevation of GA, 2-hydroxy glutaric acid (2OH-GA), 3OH-GA, EMA, and MSA are consistent with a diagnosis of glutaric acidemia (GA-2).

**Reference Values:**
- 2-OH Glutaric acid \(< or = 4.5\) nmol/mL
- 3-OH Glutaric acid \(< or = 0.7\) nmol/mL
- Glutaric acid \(< or = 0.8\) nmol/mL
- Methylsuccinic acid \(< or = 0.3\) nmol/mL
- Ethylmalonic acid \(< or = 1.5\) nmol/mL

**Clinical References:**

**Clinical Information:**
Acylcarnitine analysis is included in newborn screening blood testing and is utilized for detection of several inborn errors of metabolism, including fatty acid oxidation disorders (FAOD) and organic acidemias (OA). A limitation of this analytic method is its inability to differentiate between several isomers. Additional testing of 2-hydroxy glutaric acid (2OH-GA), 3-hydroxy glutaric acid (3OH-GA), glutaric acid (GA), methylsuccinic acid (MSA), and ethylmalonic acid (EMA) by LC-MS/MS allows better differentiation among C4 acylcarnitine and glutarylcarnitine/C10-OH isomers. C4 acylcarnitine represents both butyrylcarnitine and isobutyrylcarnitine and is elevated in short chain acyl Co-A dehydrogenase (SCAD) deficiency, isobutyryl-CoA dehydrogenase (IBDH) deficiency and ethylmalonic encephalopathy (EE). SCAD deficiency is a condition affecting fatty acid metabolism, with reported symptoms of hypoglycemia, lethargy, developmental delays, and failure to thrive; there is controversy on whether a biochemical diagnosis necessarily confers clinical symptoms. IBDH deficiency is characterized by cardiomyopathy, hypotonia, and developmental delays, although many individuals with IBDH deficiency are asymptomatic. EE is a rare progressive encephalopathy associated with hypotonia, seizures, and abnormal movements. Individuals with SCAD deficiency demonstrate elevated plasma EMA and MSA levels and individuals with EE show only elevations in EMA, while individuals with IBDH deficiency do not typically have elevations in either EMA or MSA. Glutarylcarnitine (C5-DC) is elevated in glutaric acidemia type 1 (GA-1), but is not differentiated from C10-OH acylcarnitine. GA-1, also known as glutaric aciduria type 1, is caused by a deficiency of glutaryl-CoA dehydrogenase. GA-1 is characterized by bilateral striatal brain injury leading to dystonia, often a result of acute neurologic crises triggered by illness. Individuals with GA-1 typically show elevations of glutaric acid and 3OH-GA, even in those considered to be "low excretors." Glutaric acidemia (GA-2), also known as multiple acyl-CoA dehydrogenase deficiency (MADD), is caused by defects in either the electron transfer flavoprotein (ETF) or ETF-ubiquinone oxireductase. This disease can be severe and is often fatal in the first weeks of life, with typical symptoms of hypoglycemia, muscle weakness, metabolic acidosis, dysmorphic features, cardiac defects or arrhythmias, renal cysts, and fatty infiltration of the liver. GA-2 can have a milder presentation, also known as ethylmalonic-adipic aciduria, with Reye-like illnesses in childhood, and muscle weakness in childhood and adulthood. In addition to elevations in glutaric acid, individuals with GA-2 can also show increased EMA, MSA, and 2OH-GA. The American College of Medical Genetics (ACMG) newborn screening work group published diagnostic algorithms for the follow-up of infants who had a positive newborn screening result. For more information, see www.acmg.net.

**Useful For:**
Evaluation of patients with an abnormal newborn screen showing elevations of glutarylcarnitine (C5-DC) Evaluation of patients with abnormal newborn screens showing elevations of C4 acylcarnitine to aid in the differential diagnosis of short chain acyl-CoA dehydrogenase and isobutyryl-CoA dehydrogenase deficiencies Diagnosis of glutaric acidemia type 1 Aids in diagnosis of glutaric acidemia type 2
**Interpretation:** Elevations of ethylmalonic acid (EMA) and methylsuccinic acid (MSA) are consistent with a diagnosis of short chain acyl Co-A dehydrogenase (SCAD) deficiency. Elevation of EMA is consistent with a diagnosis of ethylmalonic encephalopathy. Normal levels of EMA in the context of elevated C4 is consistent with a diagnosis of isobutyryl-CoA dehydrogenase (IBDH) deficiency. Elevation of glutaric acid (GA) and 3-hydroxy glutaric acid (3OH-GA) are consistent with a diagnosis of glutaric acidemia type 1 (GA-1). Elevation of GA, 2-hydroxy glutaric acid (2OH-GA), 3OH-GA, EMA, and MSA are consistent with a diagnosis of glutaric acidemia (GA-2).

**Reference Values:**
- 2-OH Glutaric acid < or = 4.5 nmol/mL
- 3-OH Glutaric acid < or = 0.7 nmol/mL
- Glutaric acid < or = 0.8 nmol/mL
- Methylsuccinic acid < or = 0.3 nmol/mL
- Ethylmalonic acid < or = 1.5 nmol/mL

**Clinical References:**

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**FVIST**

**Hydroxyzine (Vistaril, Atarax), Serum**

**Reference Values:**
Reference Range: 10 - 100 ng/mL

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**HYOX**

**Hyperoxaluria Panel, Urine**

**Clinical Information:** Increased urinary oxalate frequently leads to renal stone formation and renal insufficiency. Identifying the cause of hyperoxaluria has important implications in therapy, management and prognosis. Hyperoxalurias are classified as primary and secondary. Primary hyperoxaluria is an inherited disorder of oxalate metabolism while secondary hyperoxaluria is an acquired condition resulting from either increased intake of dietary oxalate or altered intestinal oxalate absorption. Primary hyperoxalurias are classified into types 1, 2, and 3. Type 1 (PH1), an autosomal recessive deficiency of peroxisomal alanine: glyoxylate aminotransferase due to mutations in the AGXT gene, is characterized by increased urinary oxalic, glyoxylic, and glycolic acids. PH1 is the most common with manifestations that include deposition of calcium oxalate in the kidneys (nephrolithiasis, nephrocalcinosis), and end-stage renal disease. Calcium oxalate deposits can be further deposited in other tissues such as the heart and eyes, and lead to a variety of additional symptoms. Age of onset is variable with a small percentage of patients presenting in the first year of life with failure to thrive, nephrocalcinosis, and metabolic acidosis. Approximately half of affected individuals show manifestations of PH1 in late childhood or early adolescence, and the remainder present in adulthood with recurrent renal stones. Some individuals with PH1 respond to supplementary pyridoxine therapy. Hyperoxaluria type 2 (PH 2) is due to a defect in GRHPR gene resulting in a deficiency of the enzyme hydroxypropyruvate reductase. PH2 is autosomal recessive and identified by an increase in urinary oxalic and glyceric acids. Like PH1, PH2 is characterized by deposition of calcium oxalate in the kidneys (nephrolithiasis, nephrocalcinosis), and end-stage renal disease. Most individuals have symptoms of PH2 during childhood, and it is thought that PH2 is less common than PH1. Hyperoxaluria type 3 (PH3), due to recessive mutations in HOGA1 (formerly DHDPDSL), occurs in a small percentage of individuals with primary hyperoxaluria. HOGA1 encodes a mitochondrial 4-hydroxy-2-oxoglutarate aldolase that catalyzes the 4th step in the hydroxyproline pathway. PH3 is characterized biochemically by increased urinary excretion of oxalate and 4-hydroxy-2-oxoglutarate (HOG). As with PH types 1 and 2, PH type 3 is characterized by calcium-oxalate deposition in the kidneys and/or kidney stone formation. Most individuals with PH3
have early onset disease with recurrent kidney stones and urinary tract infections as common symptoms. End-stage renal disease is not a characteristic of PH3. Of note, individuals with heterozygous mutations in HOGA1 can have variable and intermittent elevations of urine oxalate. Secondary hyperoxalurias are due to hyperabsorption of oxalate (enteric hyperoxaluria); total parenteral nutrition in premature infants; ingestion of oxalate, ascorbic acid, or ethylene glycol; or pyridoxine deficiency, and may respond to appropriate therapy. A diagnostic workup in an individual with hyperoxaluria demonstrates increased concentration of oxalate in urinary metabolite screening. If glycolate, glycerate, or HOG is present, a primary hyperoxaluria is indicated. Additional analyses can include molecular testing for PH1 (AGXTG / Alanine:Glyoxylate Aminotransferase (AGXT) Mutation Analysis (G170R), Blood or AGXTZ / AGXT Gene, Full Gene Analysis), PH2 (GRHPZ / GRHPR Gene, Full Gene Analysis), or PH3 (HOGA1 testing not available at Mayo at this time).

Useful For: Distinguishing between primary and secondary hyperoxaluria Distinguishing between primary hyperoxaluria types 1, 2, and 3

Interpretation: Increased concentrations of oxalate and glycolate indicate type 1 hyperoxaluria. Increased concentrations of oxalate and glycerate indicate type 2 hyperoxaluria. Increased concentrations of oxalate and 4-hydroxy-2-oxoglutarate indicate type 3 hyperoxaluria. Increased concentrations of oxalate with normal concentrations of glycolate, glycerate, and 4-hydroxy-2-oxoglutarate indicate secondary hyperoxaluria.

Reference Values:
REPORTING/INTERPRETING RESULTS
Reference Intervals (Normal Ranges):

Glycolate
< or =17 years: < or =75 mg/g creatinine
> or =18 years: < or =50 mg/g creatinine

Glycerate
< or =31 days: < or =75 mg/g creatinine
32 days - 4 years: < or =125 mg/g creatinine
5 - 10 years: < or =55 mg/g creatinine
> or =11 years: < or =25 mg/g creatinine

Oxalate
< or =6 months: < or =400 mg/g creatinine
7 months - 1 year: < or =300 mg/g creatinine
2 - 6 years: < or =150 mg/g creatinine
7 - 10 years: < or =100 mg/g creatinine
> or =11 years: < or =75 mg/g creatinine

4-hydroxy-2-oxoglutarate (HOG)
< or =10 mg/g creatinine

Clinical Information: A hypersensitivity pneumonitis (HP) due to the inhalation and sensitization to avian antigens. Immunodiffusion is used to evaluate the presence of precipitating antibodies in the sera of patients with HP due to the sensitization to various species of birds.

Reference Values:
This panel includes the following antigens:

- Pigeon Sera
- Pigeon DE
- Cockatiel
- Parakeet
- Parrot

This result must be correlated with patient's clinical response and should not solely be considered in the diagnosis.

Hypersensitivity Pneumonitis FEIA Panel II

Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:
- Alternaria tenuis/alternata IgG <12 mcg/mL
- Aspergillus fumigatus IgG <46 mcg/mL
- Aureobasidium pullulans IgG <18 mcg/mL
- Micropolyspora faeni IgG <5 mcg/mL
- Penicillium Chrysogenum/notatum IgG <22 mcg/mL
- Phoma betae IgG <8 mcg/mL
- Thermoactinomyces vulgaris IgG <13 mcg/mL
- Trichoderma viride IgG <10 mcg/mL

Antibody levels greater than the reference range indicate that the patient has been immunologically sensitized to the antigen. The significance of elevated IgG depends on the nature of the antigen and the patientâ€™s clinical history. The test method was the Phadia ImmunoCAP.

Hypersensitivity Pneumonitis Panel, IgG, Serum

Clinical Information: Hypersensitivity pneumonitis (HP) is a heterogeneous disease caused by exposure to organic dust antigens, animal proteins, chemicals, medications, or microorganisms (eg, Thermoactinomyces vulgaris, Micropolyspora faeni, Aspergillus fumigatus). The immunopathogenesis of disease is not known; but, several immunologic mechanisms may play a role in producing alveolitis, including cellular immunity mediated by CD4 and CD8 T lymphocytes, immune-complex mediated inflammation, complement activation or activation of alveolar macrophages.(1) HP is suspected clinically in patients who present with intermittent or progressive pulmonary symptoms and interstitial lung disease. The diagnosis is established by compatible clinical and radiographic findings, pulmonary function tests, and demonstration of specific antibodies to organic antigens known to cause the disease.

Useful For: Evaluation of patients suspected of having hypersensitivity pneumonitis induced by exposure to Aspergillus fumigatus, Thermoactinomyces vulgaris, or Micropolyspora faeni

Interpretation: Elevated concentrations of IgG antibodies to Aspergillus fumigatus, Thermoactinomyces vulgaris, or Micropolyspora faeni in patients with signs and symptoms of hypersensitivity pneumonitis may be consistent with disease caused by exposure to 1 or more of these organic antigens.

Reference Values:
- Aspergillus fumigatus, IgG ANTIBODIES <4 years: not established
> or =4 years: < or =102 mg/L
Micropolyspora faeni, IgG ANTIBODIES
0-12 years: < or =4.9 mg/L
13-18 years: < or =9.1 mg/L
>18 years: < or =13.2 mg/L
Thermoactinomycyes vulgaris, IgG ANTIBODIES
0-12 years: < or =6.6 mg/L
13-18 years: < or =11.0 mg/L
>18 years: < or =23.9 mg/L


Hypertrophic Cardiomyopathy Multi-Gene Panel, Blood

Clinical Information: The cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathy can be caused by inherited, genetic factors, or by nongenetic (acquired) causes such as infection or trauma. When the presence or severity of the cardiomyopathy observed in a patient cannot be explained by acquired causes, genetic testing for the inherited forms of cardiomyopathy may be considered. Overall, the cardiomyopathies are some of the most common genetic disorders. The inherited forms of cardiomyopathy include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and left ventricular noncompaction (LVNC). The hereditary form of HCM is characterized by left ventricular hypertrophy in the absence of other cardiac or systemic causes that may cause hypertrophy of the heart muscle, such as longstanding, uncontrolled hypertension or aortic stenosis. The pathological hallmark of HCM is "myocyte disarray" where there is a loss of parallel alignment of myocytes in the heart wall. HCM is most often caused by genes encoding the cardiac sarcomere, the functional contractile unit of the heart muscle. The clinical presentation of HCM can be variable, even within the same family. HCM can be asymptomatic in some individuals, but can cause life-threatening arrhythmias, which increase the risk of sudden cardiac death. The incidence of HCM in the general population is approximately 1 in 500. Inheritance is autosomal dominant, but compound heterozygosity (biallelic variants in the same gene) and digenic inheritance (variants in 2 different HCM-associated genes) do occur. The MYBPC3, MYL2, MYL3, MYH7, ACTC, TPM1, TNNT3, TNNT2, and CAV3 genes are involved in formation and regulation of the cardiac sarcomere, and account for the majority of variants in HCM. Left ventricular hypertrophy can also be caused by metabolic or storage disorders such as Fabry disease (GLA gene), Danon disease (LAMP2 gene), and Wolf-Parkinson-White syndrome associated with variants in the PRKAG2 gene. The TTR gene causes familial transthyretin amyloidosis, which is characterized by buildup of amyloid protein that affects the peripheral and autonomic nervous system. Other nonneuropathic changes may also be involved, including cardiomyopathy. See table for details regarding the genes tested by this panel and associated diseases. Genes included in the Hypertrophic Cardiomyopathy Multi-Gene Panel Gene Protein Inheritance Disease Association ACTC1 Actin, alpha, cardiac muscle AD CHD, DCM, HCM, LVNC ACTN2 Actinin, alpha-2 AD DCM, HCM ANKR1A Ankyrin repeat domain-containing protein 1 AD HCM, DCM CAV3 Caveolin 3 AD, AR HCM, LQTS, LGMD, Tageyama-type distal myopathy, rippling muscle disease CSRPR3 Cysteine-and glycine-rich protein 3 AD HCM, DCM DES Desmin AD, AR DCM, ARVC, myofibrillar myopathy, RCM with AV block, neurogenic scapuloperoneal syndrome Kaeser type, LGMD GLA Galactosidase, alpha X-linked Fabry disease LAMP2 Lysosome-associated membrane protein 2 X-linked Danon disease MYBP3 Myosin-binding protein-C, cardiac AD HCM, DCM MYH7 Myosin, heavy chain 7, cardiac muscle, beta AD HCM, DCM, LVNC, myopathy MYL2 Myosin, light chain 2, regulatory, cardiac, slow AD HCM MYL3 Myosin, light chain 3, alkali, ventricular, skeletal, slow AD, AR HCM MYLK2 Myosin light chain kinase 2 AD HCM MYOZ2 Myozin 2 AD HCM NEXN Nexilin AD HCM, DCM PLN Phospholamban AD HCM, DCM PRKAG2 Protein kinase, amp-activated, noncatalytic, gamma2 AD HCM, Wolff-Parkinson-White syndrome RAF1 V-RAF-1 murine leukemia viral oncogene homolog 1 AD Noonan/multiple lentigines syndrome TCAP Titin-cap
(telethonin) AD, AR HCM, DCM, LGMD TNNC1 Troponin C, slow AD HCM, DCM TNNI3 Troponin I, cardiac AD, AR DCM, HCM, RCMD TNNT2 Troponin T2, cardiac AD HCM, DCM, RCMD, LVNC TPM1 Tropomyosin 1 AD HCM, DCM, LVNC TTN Titin AD, AR HCM, DCM, myopathy TTR Transthyretin AD Transthyretin-related amyloidosis VCL Vinculin AD HCM, DCM Abbreviations: Congenital heart defects (CHD), long QT syndrome (LQTS), limb-girdle muscular dystrophy (LGMD), autosomal dominant (AD), autosomal recessive (AR)

**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of hereditary hypertrophic cardiomyopathy (HCM) Establishing a diagnosis of a hereditary HCM, and in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying a pathogenic variant within a gene known to be associated with disease that allows for predictive testing of at-risk family members

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**HYPOG 82439**

**Hypoglycemic Agent Screen, Serum**

**Clinical Information:** The metabolic and hormonal profiles of insulinoma and sulfonylurea-induced hypoglycemia are identical. Therefore, in the evaluation of the hypoglycemic patient, the possible use of oral hypoglycemic agents as the cause for low blood glucose and elevated plasma insulin must be considered. Absence of hypoglycemic drugs in blood serum during an episode of low blood glucose should be demonstrated before considering pancreatic exploration for suspected insulinoma.

**Useful For:** Evaluation of suspected insulinoma characterized by hypoglycemia and increased plasma insulin concentration. Detecting drugs that stimulate insulin secretion If hypoglycemia is the result of 1 of these drugs, the test will detect the drug at physiologically significant concentrations in serum during an episode of hypoglycemia. Drugs detected by this procedure are: -The first-generation sulfonylureas-acetohexamide, chlorpropamide, tolazamide, and tolbutamide -The second-generation sulfonylureas-glimepiride, glipizide, and glyburide -The meglitinide-repaglinide Drugs designed to
make tissues more sensitive to insulin that do not induce hypoglycemia, such as pioglitazone, rosiglitazone, and troglitazone (recently withdrawn from the United States market) are not included in this screen test. Drugs that lower blood glucose through mechanisms not related to stimulation of insulin secretion, such as acarbose, metformin, and miglitol are not included in this screen test.

**Interpretation:** Use of hypoglycemic agents outside of the context of treatment of type 2 diabetes is likely to cause hypoglycemia associated with elevated plasma insulin. Patients presenting with hypoglycemia due to ingestion of a first-, second-, or third-generation hypoglycemic agent will have drug present in serum greater than the minimum effective concentration (see Reference Values). Presence of drug indicates that the patient has recently ingested a hypoglycemic agent.

**Reference Values:**

- **ACETOHEXAMIDE**
  - Negative: <1,000 ng/mL

- **CHLORPROPAMIDE**
  - Negative: <1,000 ng/mL

- **TOLAZAMIDE**
  - Negative: <20 ng/mL

- **TOLBUTAMIDE**
  - Negative: <50 ng/mL

- **GLIMEPIRIDE**
  - Negative: <20 ng/mL

- **GLIPIZIDE**
  - Negative: <3 ng/mL

- **GLYBURIDE**
  - Negative: <3 ng/mL

- **REPAGLINIDE**
  - Negative: <3 ng/mL
  - Note: The report indicates a specific drug is positive if that drug is detected at a concentration greater than the sensitivity limit. The test sensitivity limit listed for each drug is lower than the concentration that will cause increased insulin and decreased glucose.


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**HIF2A**

**Hypoxia-Inducible Factor Alpha (EPAS1/HIF2A) Gene, Exons 9 and 12 Sequencing**

**Clinical Information:** Erythrocytosis (ie, increased RBC mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, polycythemia vera: PV), or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other EPO-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be suspected. Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases is associated with pheochromocytoma and/or paraganglioma formation. It is caused by mutations in several genes and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these cases, although it is possible for new mutations to arise in an
individual. The genes coding for hemoglobin, beta globin and alpha globin (high-oxygen-affinity hemoglobin variants), hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase: BPGM), and the erythropoietin receptor, EPOR, and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF/EPAS1, prolyl hydroxylase domain: PHD2/EGLN1, and von Hippel Lindau: VHL) can result in hereditary erythrocytosis (see Table). High-oxygen-affinity hemoglobin variants and BPGM abnormalities result in a decreased p50 result, whereas those affecting EPOR, HIF, PHD, and VHL have normal p50 results. The true prevalence of hereditary erythrocytosis-causing mutations is unknown.

<table>
<thead>
<tr>
<th>Genes Associated with Hereditary Erythrocytosis</th>
<th>Gene Inheritance</th>
<th>Serum EPO</th>
<th>p50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired Decreased Normal JAK2 V617F</td>
<td>Decreased</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Acquired Decreased Normal EPOR Dominant</td>
<td>Decreased</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Acquired Decreased Normal PHD2/EGLN1 Dominant</td>
<td>Decreased</td>
<td>Normal</td>
<td></td>
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<tr>
<td>Acquired Decreased Normal BPGM Recessive</td>
<td>Decreased</td>
<td>Normal</td>
<td></td>
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<tr>
<td>Acquired Decreased Normal Beta Globin Dominant</td>
<td>Decreased</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Acquired Decreased Normal HIF2A/EPAS1 Dominant</td>
<td>Decreased</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Acquired Decreased Normal VHL Recessive</td>
<td>Decreased</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>

The oxygen-sensing pathway functions through an enzyme, hypoxia-inducible factor (HIF), which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including EPO, VEGF, and GLUT1. HIF-alpha is regulated by von Hippel-Lindau (VHL) protein-mediated ubiquitination and proteosomal degradation, which requires prolyl hydroxylation of HIF proline residues. The HIF-alpha subunit is encoded by the HIF2A (official name EPAS1) gene. Enzymes important in the hydroxylation of HIF-alpha are the prolyl hydroxylase domain proteins, of which the most significant isoform is PHD2, which is encoded by the PHD2 (official name EGLN1) gene. Mutations resulting in altered HIF-alpha, PHD2, and VHL proteins can lead to clinical erythrocytosis. A small subset of mutations, in PHD2 and HIF2A, has also been detected in erythrocytic patients presenting with paragangliomas or pheochromocytomas. Truncating mutations in the EPOR gene coding for the erythropoietin receptor can result in erythrocytosis through loss of the negative regulatory cytoplasmic SHP-1 binding domain leading to EPO hypersensitivity. All currently known mutations have been localized to exon 8, are mainly missense or small deletion and insertions resulting in stop codons, and are heterozygous. EPOR mutations are associated with decreased to normal EPO levels and normal p50 values (see Table).

Useful For: The definitive evaluation of an individual with JAK2-negative erythrocytosis associated with lifelong sustained increased RBC mass, elevated RBC count, hemoglobin, or hematocrit

Interpretation: An interpretive report will be provided as a part of the HEMP / Hereditary Erythrocytosis Mutations, and will include specimen information, assay information, and whether the specimen was positive for any mutations in the gene. If positive, the mutation will be correlated with clinical significance, if known.

Reference Values: Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations.

An interpretive report will be provided.

Clinical References:

**ICOS (CD278), Immunostain, Technical Component Only**

**Clinical Information:** ICOS (CD278) is primarily expressed on activated CD4+ and CD8+ T cells where it regulates immune responses and plays a role in the regulation of T follicular helper cells. ICOS is a sensitive marker for identifying T cell lymphomas of follicular helper T cell origin, especially...
certain patterns of angioimmunoblastic T-cell lymphoma (AITL) and peripheral T-cell lymphomas with T-follicular helper phenotype (PTCL-TFH). This is becoming increasingly important given WHO 2016 diagnostic guidelines.

Useful For: Aiding in the classification of T cell lymphomas

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist is required order PATHC / Pathology Consultation. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


LCHB 60214
Id, Histoplasma/Blastomyces PCR (Bill Only)
Reference Values:
This test is for billing purposes only. This is not an orderable test.

RMALD 60029
Ident by MALDI-TOF Mass Spec (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

LCCI 45463
Ident Rapid PCR Coccidioides (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

PCRID 64706
Identification by PCR (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IDH1 70468
IDH1 Mutation (R132H) Immunostain, Technical Component Only
Clinical Information: Antihuman isocitrate dehydrogenase 1 (IDH1) R132H antibody binds to IDH1-mutated protein, but does not bind the wild-type IDH1 protein. IDH1 R132H point mutations are frequently seen in World Health Organization grade II and III gliomas and are believed to constitute an
early step in tumorigenesis. IDH1 R132H can be used as a diagnostic marker to help differentiate infiltrating gliomas from gliosis, and as a prognostic marker for gliomas and secondary glioblastoma multiforme. IDH1 R132H antibody shows strong cytoplasmic staining and weaker nuclear staining in tumor cells with the R132H-mutated peptide. Diffuse staining of the fibrillary tumor matrix is also seen.

**Useful For:** Aids in the classification of gliomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Iduronate-2-Sulfatase, Blood Spot**

**Clinical Information:** The mucopolysaccharidoses are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate, also known as glycosaminoglycans (GAGs). Accumulation of GAGs in the lysosomes interferes with normal functioning of cells, tissues, and organs. Mucopolysaccharidosis II, (MPS II, Hunter syndrome) is an X-linked lysosomal storage disorder caused by the deficiency of iduronate sulfatase (IDS) enzyme and gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms are widely variable ranging from severe, infantile onset disease to an attenuated form, which generally has a later onset with a milder clinical presentation. Symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. As an X-linked disorder, Hunter disease occurs primarily in males with an estimated incidence of 1 in 120,000 male births, although symptomatic carrier females have been reported. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. A diagnostic workup in an individual with MPS II typically demonstrates elevated levels of urinary glycosaminoglycans and increased amounts of both dermatan and heparan sulfate. Reduced or absent activity of IDS can confirm a diagnosis of MPS II; however, enzymatic testing is not reliable to detect carriers. Molecular genetic testing of the IDS gene allows for detection of the disease-causing mutation in affected patients and subsequent carrier detection in female relatives. Currently, no clear genotype-phenotype correlations have been established.

**Useful For:** Diagnosis of mucopolysaccharidosis II (MPS II, Hunter syndrome) using dried blood spot specimens

**Interpretation:** Specimens with results below 1.5 nmol/hour/mL in properly submitted specimens
are consistent with iduronate-2-sulfatase deficiency (mucopolysaccharidosis II: MPS II). If clinically indicated, consider further confirmation by molecular genetic analysis of the IDS gene. Please note that this enzyme’s activity can also be reduced in multiple sulfatase deficiency. If clinically indicated, consider biochemical genetic testing of other sulfatases or molecular genetic testing of the SUMF1 gene to exclude MSD. Normal results (> or =1.5 nmol/h/mL) are not consistent with iduronate-2-sulfatase deficiency.

**Reference Values:**
> or =1.5 nmol/h/mL

**Clinical References:**
IGAI
70470
IgA Immunostain, Technical Component Only

Clinical Information: The immunoglobulin molecules (antibodies) function as the surface receptors for antigens for B lymphocytes and as the secretory products of plasma cells forming the humoral arm of the immune system. IgA represents one of the immunoglobulin heavy chain types and is the major immunoglobulin class secreted at mucosal surfaces. Diagnostically, staining for immunoglobulin heavy chains can aid in the diagnosis and classification of small B-cell malignant lymphomas and multiple myeloma.

Useful For: Aids in the classification of lymphomas and multiple myeloma

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


IGAS
87938
IgA Subclasses, Serum

Clinical Information: IgA, the predominant immunoglobulin secreted at mucosal surfaces, consists of 2 subclasses, IgA1 and IgA2. IgA1 is the major (approximately 80%) subclass in serum. IgA2 is the major subclass in secretions such as milk. Although IgA deficiency is a common defect (1 in 700), it is usually asymptomatic. IgA deficiency with or without IgG subclass deficiency, however, can lead to...
recurrent pulmonary and gastrointestinal infections. Some infections (e.g., recurrent sinopulmonary infections with Haemophilus influenzae) may be related to a deficiency of IgA2 in the presence of normal total IgA concentrations. Paradoxically, bacterial infections may also cause IgA deficiency. For example, IgA1 (but not IgA2) can be cleaved and inactivated by certain bacteria, thus depleting the majority of the IgA. In the presence of a concurrent IgA2 deficiency, infection by these organisms results in an apparent IgA deficiency. IgA deficiency is 1 cause of anaphylactic transfusion reactions. In these situations, IgA-deficient patients produce anti-IgA antibodies that react with IgA present in the transfusion product. While transfusion reactions typically occur in patients who have no detectable levels of IgA, they can occur in patients with measurable IgA. In these situations, the complete deficiency of 1 of the IgA subclasses may be the cause of the transfusion reactions.

**Useful For:** Investigation of immune deficiency due to IgA2 deficiency Evaluating patients with anaphylactic transfusion reactions

**Interpretation:** Low concentrations of IgA2 with normal IgA1 levels suggest an IgA2 deficiency. Elevated concentrations of IgA2 with normal or low amounts of IgA1 suggest a clonal plasma cell proliferative disorder secreting a monoclonal IgA2. Increased total IgA levels also may be seen in benign disorders (e.g., infection, inflammation, allergy), hyper IgD syndrome with periodic fever and monoclonal gammopathies (e.g., myeloma, monoclonal gammopathies of undetermined significance [MGUS]).

**Reference Values:**

**IgA**

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<tr>
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<td>7-37 mg/dL</td>
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<td>61-356 mg/dL</td>
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**IgA1**

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</tr>
</thead>
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<td>15-&lt;24 months</td>
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**IgA2**

<table>
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<tbody>
<tr>
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<td>6.6-54.3 mg/dL</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td>9.7-156.0 mg/dL</td>
</tr>
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</table>

**IGD Immunostain, Technical Component Only**

**Clinical Information:** The immunoglobulin molecules (antibodies) function as the surface receptors for antigens for B lymphocytes and as the secretory products of plasma cells forming the humoral arm of the immune system. IgD represents one of the immunoglobulin heavy chain types. Immunoreactivity is a specific marker for B lymphocytes and plasma cells; it is expressed normally on mantle zone lymphocytes. Diagnostically, staining for immunoglobulin heavy chains can aid in the diagnosis and classification of small B cell malignant lymphomas and multiple myeloma.

**Useful For:** Aids in the classification of lymphomas and multiple myeloma

**Interpretation:** The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**FGERA**

**IgE Receptor Antibody**

**Useful For:** The test detects functional autoantibodies to the Fc-epsilon receptor (high affinity IgE receptor) or to IgE and is useful in the evaluation of chronic urticaria.

**Interpretation:** Chronic autoimmune urticaria (CIU) may be associated with autoantibodies to the high affinity IgE receptor (Fc-epsilon R1) or to IgE. In the presence of the autoantibodies, cross-linking of the Fc-epsilon-R1 receptor occurs, leading to basophil activation. The laboratory tests for the activation of donor basophils by CIU serum by analyzing the expression of the basophil specific ectoenzyme, CD203c. CD203c is upregulated on the surface of basophils following activation. A positive result is indicative of the presence of autoantibodies associated with CIU, but may also be due to other basophil-activating serum factors. Results must be correlated with clinical findings. The reference range was developed by the National Jewish Health Advanced Diagnostic Laboratories by analyzing 80 healthy control serum samples.

**Reference Values:**

0 - 12


**FIGBP**

**IGF Binding Protein-1 (IGFBP-1)**

**Reference Values:**
IGGI

IgG Immunostain, Technical Component Only

Clinical Information: The immunoglobulin molecules (antibodies) function as the surface receptors for antigens for B lymphocytes and as the secretory products of plasma cells forming the humoral arm of the immune system. IgG represents one of the immunoglobulin heavy chain types. Immunoreactivity is a specific marker for B lymphocytes and plasma cells. Diagnostically, staining for immunoglobulin heavy chains can aid in the diagnosis and classification of small B cell malignant lymphomas and multiple myeloma.

Useful For: Aids in the classification of lymphomas and multiple myeloma

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


IGGS

IgG Subclasses, Serum

Clinical Information: The most abundant immunoglobulin in human serum is immunoglobulin G (IgG) (approximately 80% of the total). IgG protein is comprised of molecules of 4 subclasses designated IgG1 through IgG4. Each subclass contains molecules with a structurally unique gamma heavy chain. Of total IgG, approximately 65% is IgG1, 25% is IgG2, 6% is IgG3, and 4% is IgG4. Molecules of different IgG subclasses have somewhat different biologic properties (eg, complement fixing ability and binding to phagocytic cells), which are determined by structural differences in gamma heavy chains. Clinical interest in IgG subclasses concerns potential immunodeficiencies (eg, subclass deficiencies) and IgG4-related diseases (eg, IgG4 elevations). The IgG subclass assay (IGGS / IgG Subclasses, Serum) is best for deficiency testing, and the IgG4 assay (IGGS4 / Immunoglobulin Subclass IgG4, Serum) is best for
IgG4-related disease testing. Diminished concentrations of IgG subclass proteins may occur in the context of hypogammaglobulinemia (eg, in common variable immunodeficiency where all immunoglobulin classes are generally affected) or deficiencies may be selective, usually involving IgG2. Deficiency of IgG1 usually occurs in patients with severe immunoglobulin deficiency involving other IgG subclasses. Deficiency of IgG2 is more heterogeneous and can occur as an isolated deficiency or in combination with deficiency of immunoglobulin A (IgA), or of IgA and other IgG subclasses. Most patients with IgG2 deficiency present with recurrent infections, usually sinusitis, otitis, or pulmonary infections. Children with deficiency of IgG2 often have deficient antibody responses to polysaccharide antigens including bacterial antigens associated with Haemophilus influenzae type B and Streptococcus pneumoniae. Isolated deficiencies of IgG3 or IgG4 occur rarely, and the clinical significance of these findings is not clear. IgG subclass 4-related disease is a recently recognized syndrome of unknown etiology most often occurring in middle-aged and older men. Several organ systems can be involved and encompasses many previous and newly described diseases such as type 1 autoimmune pancreatitis; Mikulicz disease and sclerosing sialadenitis; inflammatory orbital pseudotumor; chronic sclerosing aortitis; Riedel thyroiditis, a subset of Hashimoto thyroiditis; IgG4-related interstitial pneumonitis; and IgG4-related tubulointerstitial nephritis. Each of these entities is characterized by tumor-like swelling of the involved organs with infiltrative, predominately IgG4-positive, plasma cells with accompanying "storiform" fibrosis. In addition, elevated serum concentrations of IgG4 are found in 60% to 70% of patients diagnosed with IgG4-related disease. The diagnosis of IgG4-related disease requires a tissue biopsy of the affected organ demonstrating the aforementioned histological features. It is recommended that patients suspected of having an IgG4-related disease have their serum IgG4 level measured. Testing for immunoglobulin G (IgG) subclass levels may be indicated in patients with clinical evidence of a possible immunodeficiency with hypogammaglobulinemic patients or normal concentrations of total serum IgG.

**Useful For:** Second-order testing for evaluation of patients with clinical signs and symptoms of humoral immunodeficiency or combined immunodeficiency (cellular and humoral)

**Interpretation:** Diminished concentrations of all immunoglobulin G (IgG) subclasses are found in common variable immunodeficiency, combined immunodeficiency, ataxia telangiectasia, and other primary and acquired immunodeficiency diseases. A diminished concentration of IgG2 protein may be clinically significant in the context of recurrent sinopulmonary infection and may occur with or without concomitant immunoglobulin A deficiency. Elevated levels of IgG4 are consistent with, but not diagnostic of, IgG4-related disease. Slightly diminished concentrations of 1 or more IgG subclass proteins are not uncommon, and usually have little clinical significance. Conversely, some individuals with deficient specific antibody responses to polysaccharide antigens may have normal serum levels of IgG subclasses.

**Reference Values:**

**TOTAL IgG**

<table>
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<th>Age Group</th>
<th>Reference Range</th>
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<td>100-334 mg/dL</td>
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<td>5-&lt;9 months</td>
<td>164-588 mg/dL</td>
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<td>9-&lt;15 months</td>
<td>246-904 mg/dL</td>
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<td>15-&lt;24 months</td>
<td>313-1,170 mg/dL</td>
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<td>2-&lt;4 years</td>
<td>295-1,156 mg/dL</td>
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<td>4-&lt;7 years</td>
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<td>7-&lt;10 years</td>
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<tr>
<td>&gt; or =18 years</td>
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**IgG1**

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<td>5-&lt;9 months</td>
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<td>9-&lt;15 months</td>
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<td>209-724 mg/dL</td>
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<td>2-&lt;4 years</td>
<td>158-721 mg/dL</td>
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<td>4-&lt;7 years</td>
<td>209-902 mg/dL</td>
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<tr>
<td>7-&lt;10 years</td>
<td>253-1,019 mg/dL</td>
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</tbody>
</table>
10-<13 years: 280-1030 mg/dL
13-<16 years: 289-934 mg/dL
16-<18 years: 283-772 mg/dL
> or =18 years: 341-894 mg/dL

IgG2
0-<5 months: < or =82 mg/dL
5-<9 months: < or =89 mg/dL
9-<15 months: 24-98 mg/dL
15-<24 months: 35-105 mg/dL
2-<4 years: 39-176 mg/dL
4-<7 years: 44-316 mg/dL
7-<10 years: 54-435 mg/dL
10-<13 years: 66-502 mg/dL
13-<16 years: 82-516 mg/dL
16-<18 years: 98-486 mg/dL
> or =18 years: 171-632 mg/dL

IgG3
0-<5 months: 7.6-82.3 mg/dL
5-<9 months: 11.9-74.0 mg/dL
9-<15 months: 17.3-63.7 mg/dL
15-<24 months: 21.9-55.0 mg/dL
2-<4 years: 17.0-84.7 mg/dL
4-<7 years: 10.8-94.9 mg/dL
7-<10 years: 8.5-102.6 mg/dL
10-<13 years: 11.5-105.3 mg/dL
13-<16 years: 20.0-103.2 mg/dL
16-<18 years: 31.3-97.6 mg/dL
> or =18 years: 18.4-106.0 mg/dL

IgG4
0-<5 months: < or =19.8 mg/dL
5-<9 months: < or =20.8 mg/dL
9-<15 months: < or =22.0 mg/dL
15-<24 months: < or =23.0 mg/dL
2-<4 years: 0.4-49.1 mg/dL
4-<7 years: 0.8-81.9 mg/dL
7-<10 years: 1.0-108.7 mg/dL
10-<13 years: 1.0-121.9 mg/dL
13-<16 years: 0.7-121.7 mg/dL
16-<18 years: 0.3-111.0 mg/dL
> or =18 years: 2.4-121.0 mg/dL


IGG Subtypes Immunofluorescence, (IGG1, IGG2, IGG3, IGG4), Tissue

Clinical Information: IgG subtypes are helpful in confirming some disease processes affecting the kidney.

Useful For: Determining the subclass of IgG antibody found in renal immunofluorescent panel and determining if the deposits are monoclonal or monotypic
**IgG/Albumin Ratio, Spinal Fluid**

**Clinical Information:** Elevation of IgG levels in the cerebrospinal fluid (CSF) of patients with inflammatory diseases of the central nervous system (CNS) (multiple sclerosis, neurosyphilis, acute inflammatory polyradiculoneuropathy, subacute sclerosing panencephalitis) is due to local (CNS) synthesis of IgG. The two most commonly used diagnostic laboratory tests for multiple sclerosis are CSF index and oligoclonal banding. The CSF index is the CSF IgG to CSF albumin ratio compared to the serum IgG to serum albumin ratio. The CSF index is therefore an indicator of the relative amount of CSF IgG compared to serum and any increase in the index is a reflection of IgG production in the central nervous system. The IgG synthesis rate is a mathematical manipulation of the CSF index data and can also be used as a marker for CNS inflammatory diseases.

**Useful For:** The cerebrospinal fluid (CSF) index is useful in the diagnosis of individuals with multiple sclerosis. In the absence of a paired CSF and serum specimen, the CSF IgG/albumin ratio can be assessed. The index is independent of the activity of the demyelinating process.

**Interpretation:** Cerebrospinal fluid IgG index is positive (elevated) in approximately 80% of patients with multiple sclerosis.

**Reference Values:**
- CSF IgG: 0.0-8.1 mg/dL
- CSF albumin: 0.0-27.0 mg/dL
- CSF IgG/albumin: 0.00-0.21

**Clinical References:**

**IgG4 Food Panel I**

**Reference Values:**
- Alpha Lactalbumin IgG4 <0.15
- Beef IgG4 <0.15
- Casein IgG4 <0.15
- Chicken IgG4 <0.15
- Corn IgG4 <0.15
- Egg Whole IgG4 <0.15
- Milk Cow IgG4 <0.15
- Potato White IgG4 <0.15
- Soybean IgG4 <0.15
- Wheat IgG4 <0.15

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization to the food allergen in question.
**FGFP2 57904**

**IgG4 Food Panel II**

**Reference Values:**
- Banana IgG4
- Chocolate/Cacao IgG4
- Milk Goat IgG4
- Oat IgG4
- Orange IgG4
- Peanut IgG4
- Pork IgG4
- Rice IgG4
- Tomato IgG4

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization to the food allergen in question.

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**FG4FP 57591**

**IgG4 Food Panel VIII**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 0.15 Upper Limit of Quantitation 30.0

**Reference Values:**
- Corn IgG4 <0.15 mcg/mL
- Egg White IgG4 <0.15 mcg/mL
- Milk Cow IgG4 <0.15 mcg/mL
- Peanut IgG4 <0.15 mcg/mL
- Soybean IgG4 <0.15 mcg/mL
- Wheat IgG4 <0.15 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG4 tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**IGG4I 70472**

**IgG4 Immunostain, Technical Component Only**

**Clinical Information:** IgG4 is the least abundant of IgG subclasses, normally comprising 6% of total IgG. Elevated serum IgG4 levels may be associated with localized or systemic allergic and autoimmune manifestations, such as inflammatory pseudotumor in liver, breast, and lung, sclerosing pancreatitis, and pemphigus vulgaris. In these disease states, increased numbers of IgG4-positive plasma cells are present.
in the tissue.

**Useful For:** Aids in the identification of IgG4-positive plasma cells in the tissue of patients with systemic autoimmune or allergic manifestations

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:** Klimstra DS, Adsay NV: Lymphoplasmacytic sclerosing (autoimmune) pancreatitis. Semin Diagn Pathol 2004 November;21(4):237-246

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**IGH Somatic Hypermutation Analysis, B-Cell Chronic Lymphocytic Leukemia (B-CLL)**

**Clinical Information:** During early B-cell development, IGH genes are assembled from multiple polymorphic gene segments that undergo rearrangements and selection, generating VDJ combinations that are unique in both length and sequence for each B cell. In addition, new acquired (somatic) point mutations are introduced into the variable (V) regions of mature B cells during the germinal center reaction in lymph nodes, and this process is called somatic hypermutation (SHM). Since chronic lymphocytic leukemia (CLL) originates from the malignant transformation of single lymphoid cells, each daughter cell shares 1 or (sometimes) more unique "clonal" antigen receptor gene rearrangements, which are cell and, therefore, tumor specific (ie, a tumor cell "fingerprint"). Clonal IGHV gene hypermutation status provides important prognostic information for patients with CLL and small lymphocytic lymphoma (SLL). The presence of IGH SHM is defined as greater than 2% difference from the germline VH gene sequence identity (mutated), whereas less than or equal to 2% difference is considered no SHM (unmutated). The status of SHM has clear influence on the median survival of CLL patients. Hypermutation of the IGH variable region is strongly predictive of a good prognosis, while lack of mutation predicts a poorer prognosis. Although the determination of mutation status can be accomplished by PCR followed by Sanger sequencing, this approach only allows for analysis of single samples at a time. Next-generation sequencing (NGS) technology (eg, using the Illumina MiSeq platform) represents a significant improvement over existing Sanger assays by allowing for batch sample analysis and simultaneous identification of clonal IGH rearrangement, the tumor-specific rearrangement sequence, and determination of somatic mutation percent.

**Useful For:** Providing prognostic information in patients with newly diagnosed B-cell chronic lymphocytic leukemia

**Interpretation:** The presence or absence of somatic hypermutation in the immunoglobulin heavy chain gene (IGH) variable (V) region DNA will be reported. A mutation frequency of greater than 2% will be reported as mutated. Both the percent mutation and the V region allele identified in the rearrangement will be included in the report. B-cell chronic lymphocytic leukemia (B-CLL) lacking somatic hypermutation of the IGHV region (unmutated) is associated with a significantly worse prognosis than B-CLL containing somatic hypermutation of the IGH region (mutated).

**Reference Values:**
An interpretive report will be provided.

**Clinical References:** 1. Hamblin TJ, Davis Z, Gardiner A, et al: Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood 1999 September
IGMI

**IgM Immunostain, Technical Component Only**

**Clinical Information:** The immunoglobulin molecules (antibodies) function as the surface receptors for antigens for B lymphocytes and as the secretory products of plasma cells forming the humoral arm of the immune system. IgM represents one of the immunoglobulin heavy chain types. IgM positive-B lymphocytes are normally present in the follicular mantle zones and germinal centers. Immunoreactivity is a specific marker for B lymphocytes and plasma cells. Diagnostically, staining for immunoglobulin heavy chains can aid in the diagnosis and classification of small B cell malignant lymphomas and multiple myeloma.

**Useful For:** Aids in the classification of lymphomas and multiple myeloma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


IHPCA

**IHC Additional (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

IHA26

**IHC Additional, Professional Only (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

IHTOA

**IHC Additional, Tech Only (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.
IHC Initial (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IHC Initial, Professional Only (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IHC Initial, Tech Only (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IHC Multiplex (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IHC Multiplex, Professional Only (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

IHC Multiplex, Tech Only (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

Imatinib Mesylate Responsive Genes, FISH
Clinical Information: Myeloid neoplasms are primary disorders of the bone marrow cells. These malignancies encompass several entities with extremely varied clinical courses, including acute myeloid leukemias (AML), chronic myeloproliferative disorders (CMPD), and myelodysplastic syndromes. The underlying genetic mechanisms associated with these malignancies are varied and only a portion of the genetic abnormalities have targeted therapies clinically available. One group of genes, including ABL1 (Abelson murine leukemia viral oncogene homolog 1), ABL2 (Abelson murine leukemia viral oncogene homolog 2), PDGFRA (platelet-derived growth factor receptor, alpha), and PDGFRB (platelet-derived growth factor receptor, beta) can be inappropriately activated via various genetic mechanisms and result in overexpression of their tyrosine kinase activity. Tyrosine kinase activity plays an important role in cellular signaling, division, and differentiation; overexpression may cause some cancers. The myeloid malignancies associated with these aberrantly expressed genes include AML, chronic myelogenous leukemia (CML), hypereosinophilic syndrome/systemic mast cell disease (HES/SMCD), and atypical...
These translocations can also be seen in lymphoid neoplasms, including acute lymphoblastic leukemia (ALL) and lymphomas, and they can also possess a varied genetic etiology. Several clinical studies have demonstrated that the malignancies displaying overexpression of these genes are responsive to imatinib mesylate, a drug that specifically targets these genes.

**Useful For:** Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with acute leukemia or other myeloid malignancies Tracking known chromosome abnormalities and response to therapy in patients with myeloid malignancies

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for any given probe. The presence of a positive clone supports a diagnosis of malignancy. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Imipramine and Desipramine, Serum**

**Clinical Information:** Imipramine and its metabolite desipramine are tricyclic antidepressants used to treat endogenous depression requiring 1 to 3 weeks of treatment before therapeutic effectiveness becomes apparent. Desipramine is used for treatment of endogenous depression when the patient needs a drug with significant stimulatory side effects. These drugs have also been employed in the treatment of enuresis (involuntary urination) in childhood and severe obsessive-compulsive neurosis. Imipramine: The optimal dosage of imipramine yields trough (just before the next dose) blood levels of imipramine and desipramine combined from 175 to 300 ng/mL. If desipramine is given, no imipramine should be detected and the therapeutic concentration for desipramine alone is 100 to 300 ng/mL. Toxicity associated with imipramine is characterized by QRS widening leading to ventricular tachycardia and asystole. In some patients, toxicity may manifest at lower concentrations, or at therapeutic concentrations in the early state of therapy. Cardiac toxicity (first-degree heart block) is usually associated with blood concentrations in excess of 400 ng/mL. Desipramine: Desipramine is the antidepressant of choice in patients where maximal stimulation is indicated. The therapeutic concentration of desipramine is 100 to 300 ng/mL. About 1 to 3 weeks of treatment are required before therapeutic effectiveness becomes apparent. The most frequent side effects are those attributable to anticholinergic effects; dry mouth, constipation, dizziness, tachycardia, palpitations, blurred vision, and urinary retention. These occur at blood concentrations in excess of 400 ng/mL, although they may occur at therapeutic concentrations in the early stage of therapy. Cardiac toxicity (first-degree heart block) is usually associated with blood concentrations in excess of 400 ng/mL.

**Useful For:** Monitoring serum concentration during therapy Evaluating potential toxicity The test may also be useful to evaluate patient compliance

**Interpretation:** Most individuals display optimal response to imipramine when combined serum levels of imipramine and desipramine are between 175 and 300 ng/mL. Risk of toxicity is increased with levels above 400ng/mL. Most individuals display optimal response to desipramine with serum levels of 100 to 300 ng/mL. Risk of toxicity is increased with desipramine levels above 400 ng/mL. Some individuals may respond well outside of these ranges, or may display toxicity within the therapeutic range, thus, interpretation should include clinical evaluation. Therapeutic ranges are based on specimen drawn at trough (ie, immediately before the next dose).

**Reference Values:**

---
IMIPRAMINE AND DESIPRAMINE
Total therapeutic concentration: 175-300 ng/mL

DESIPRAMINE ONLY
Therapeutic concentration: 100-300 ng/mL
Note: Therapeutic ranges are for specimens drawn at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.


Immunofixation Only, Serum
Clinical Information: Monoclonal gammopathies indicate a clonal expansion of plasma cells or mature B lymphocytes. The monoclonal gammopathies include diseases such as multiple myeloma, Waldenstrom’s macroglobulinemia, lymphoproliferative disease, primary systemic amyloidosis, light-chain deposition disease, as well as the premalignant disorders of smoldering myeloma and monoclonal gammopathy of undetermined significance (MGUS). Monoclonal gammopathy patients may have a relatively small monoclonal protein abnormality or a large quantifiable peak (M-spike) on serum or urine protein electrophoresis. Abnormalities detected on serum protein electrophoresis (SPEP) should be immunotyped to confirm and characterize the monoclonal protein. Immunotyping of monoclonal proteins is usually done by immunofixation electrophoresis (IFE) and identifies the monoclonal immunoglobulin heavy-chain (gamma, alpha, mu, delta, or epsilon) and/or light-chain type (kappa or lambda). It is generally recommended that both SPEP and IFE be used as a screening panel. Because IFE is more sensitive than SPEP, IFE is not only recommended as part of the initial screening process but also for confirmation of complete response to therapy.

Useful For: Identification of monoclonal immunoglobulin heavy and light chains Documentation of complete response to therapy

Interpretation: Immunofixation impression comments are made based on visual interpretation of gels.

Reference Values: No monoclonal protein detected


Immunofixation, CSF
Reference Values: Reference Range: No Monoclonal Proteins Detected

Immunoglobulin A (IgA), Serum
Clinical Information: The gamma globulin band as seen in conventional serum protein electrophoresis consists of 5 immunoglobulins. In normal serum, about 15% is immunoglobulin A (IgA). Monoclonal gammopathies of all types may lead to a spike in the gamma globulin zone seen on
serum protein electrophoresis. Monoclonal elevations of IgA characterize multiple myeloma. Decreased immunoglobulin levels are found in patients with congenital deficiencies. For your convenience, we recommend utilizing cascade testing for celiac disease. Cascade testing ensures that testing proceeds in an algorithmic fashion. The following cascades are available; select the appropriate one for your specific patient situation. Algorithms for the cascade tests are available in Special Instructions.

- CDCOM / Celiac Disease Comprehensive Cascade: complete testing including HLA DQ - CDSP / Celiac Disease Serology Cascade: complete testing excluding HLA DQ - CDGF / Celiac Disease Gluten-Free Cascade: for patients already adhering to a gluten-free diet To order individual tests, see Celiac Disease Diagnostic Testing Algorithm in Special Instructions.

Useful For: Detection or monitoring of monoclonal gammopathies and immune deficiencies

Interpretation: Increased serum immunoglobulin concentrations occur due to polyclonal or oligoclonal immunoglobulin proliferation in hepatic disease (hepatitis, liver cirrhosis), connective tissue diseases, acute and chronic infections, as well as in the cord blood of neonates with intrauterine and perinatal infections. Elevation of immunoglobulin A may occur in monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, monoclonal gammopathy of undetermined significance, and related disorders. Decreased levels are found in patients with primary or secondary immune deficiencies.

Reference Values:
- 0-<5 months: 7-37 mg/dL
- 5-<9 months: 16-50 mg/dL
- 9-<15 months: 27-66 mg/dL
- 15-<24 months: 36-79 mg/dL
- 2-<4 years: 27-246 mg/dL
- 4-<7 years: 29-256 mg/dL
- 7-<10 years: 34-274 mg/dL
- 10-<13 years: 42-295 mg/dL
- 13-<16 years: 52-319 mg/dL
- 16-<18 years: 60-337 mg/dL
- > or =18 years: 61-356 mg/dL


**Immunoglobulin D (IgD), Serum**

Clinical Information: Antibodies or immunoglobulins (Ig) are formed by plasma cells as a humoral immune response to antigens. The first antibodies formed after antigen stimulation are of the IgM class, followed later by IgG and also IgA antibodies. IgD normally occurs in serum in trace amounts. Increased serum immunoglobulin concentrations occur due to polyclonal or oligoclonal immunoglobulin proliferation in hepatic diseases (chronic hepatitis, liver cirrhosis), acute and chronic infections, autoimmune diseases, as well as in the cord blood of neonates with intrauterine and perinatal infections. Increases in serum immunoglobulin concentration are seen in monoclonal gammopathies such as multiple myeloma, Waldenstrom's macroglobulinemia, primary amyloidosis, and monoclonal gammopathy of undetermined significance. Decreased serum immunoglobulin concentrations occur in primary immunodeficiency conditions as well as in secondary immune insufficiencies including advanced monoclonal gammopathies, lymphatic leukemia, and advanced malignant tumors.
Useful For: Quantitative determination of the immunoglobulins can provide important information on the humoral immune status. Changes in IgD concentration are used as a marker of changes in the size of the clone of monoclonal IgD plasma cells.

Interpretation: The physiologic significance of serum IgD concentration is unclear and in many normal persons serum IgD is undetectable. Increased concentrations may be due to polyclonal (reactive) or monoclonal plasma cell proliferative processes. A monoclonal IgD protein is present in 1% of patients with myeloma. Monoclonal IgD proteins are often in low concentrations and do not have a quantifiable M-peak on serum protein electrophoresis. However, the presence of an IgD monoclonal protein is almost always indicative of a malignant plasma cell disorder such as multiple myeloma or primary amyloidosis.

Reference Values: < or =10 mg/dL


Immunoglobulin E (IgE), Serum

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE are generally thought of in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease, except for allergic bronchopulmonary aspergillosis (ABPA). ABPA is a hypersensitivity reaction against the fungi Aspergillus that occurs most frequently in patients with asthma or cystic fibrosis. An elevation of total IgE is part of the diagnostic criteria for ABPA, although the specific diagnostic concentration is dependent on certain patient characteristics. For patients with an established diagnosis of allergic disease, measurement of total IgE is necessary for identification of candidates for omalizumab (anti-IgE) therapy, and for determination of proper dosing. In addition to specific patient demographics and clinical presentations, candidates for omalizumab must have total IgE concentrations between 30 and 700 KU/L.

Useful For: Evaluation of patients with suspected diseases associated with elevations in total immunoglobulin E (IgE), including allergic disease, primary immunodeficiencies, infections, malignancies, or other inflammatory diseases. Diagnostic evaluation of patients with suspected allergic bronchopulmonary aspergillosis. Identification of candidates for omalizumab (anti-IgE) therapy.

Interpretation: Elevated concentrations of total immunoglobulin E (IgE) may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Elevated total IgE concentrations may be consistent with a
diagnosis of allergic bronchopulmonary aspergillosis, provided other laboratory and clinical criteria are
generated. Total IgE concentrations between 30 to 700 KU/L may identify candidates for omalizumab therapy and may help to determine proper therapeutic dosing.

**Reference Values:**  
Results Reported in kU/L

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</tbody>
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**FLCP 84190 Immunoglobulin Free Light Chains, Serum**

**Clinical Information:** The monoclonal gammopathies are characterized by a clonal expansion of plasma cells that secrete a monoclonal immunoglobulin (Ig). The monoclonal Ig secreted by these cells serves as a marker of the clonal proliferation and the quantitation of monoclonal protein can be used to monitor the disease course. The monoclonal gammopathies include multiple myeloma (MM), light chain multiple myeloma (LCMM), Waldenstrom macroglobulinemia (WM), nonsecretory myeloma (NSMM), smoldering multiple myeloma (SMM), monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis (AL), and light chain deposition disease (LCDD). Monoclonal proteins are typically detected by serum protein electrophoresis (SPEP) and immunofixation (IF). However, the monoclonal light chain diseases (LCMM, AL, LCDD) and NSMM often do not have serum monoclonal proteins in high enough concentration to be detected and quantitated by SPEP. A sensitive nephelometric assay specific for kappa free light chain (FLC) and lambda free light chain (FLC) that doesn't recognize light chains bound to Ig heavy chains has recently been described. This automated, nephelometric assay is reported to be more sensitive than IF for detection of monoclonal FLC. In some patients with NSMM, AL, or LCDD the FLC assay provides a positive identification of a monoclonal serum light chain when the serum IF is negative. In addition, the quantitation of FLC has been correlated with disease activity in patients with NSMM and AL. See Laboratory Approach to the Diagnosis of Amyloidosis and Laboratory Screening Tests for Suspected Multiple Myeloma in Special Instructions.

**Useful For:** Monitoring patients with monoclonal light chain diseases but no M-spike on protein electrophoresis

**Interpretation:** The specificity of this assay for detection of monoclonal light chains relies on the ratio of free kappa and lambda (K/L) light chains. Once an abnormal free light chain (FLC) K/L ratio has been demonstrated and a diagnosis has been made, the quantitation of the monoclonal light chain is useful for monitoring disease activity. Changes in FLC quantitation reflect changes in the size of the monoclonal...
plasma cell population. Our experience to date is limited, but changes of more than 25% or trending of multiple specimens are needed to conclude biological significance.

**Reference Values:**

**KAPPA-FREE LIGHT CHAIN**
0.33-1.94 mg/dL

**LAMBDA-FREE LIGHT CHAIN**
0.57-2.63 mg/dL

**KAPPA/LAMBDA FLC RATIO**
0.26-1.65


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**IGG**

**Immunoglobulin G (IgG), Serum**

**Clinical Information:** The gamma globulin band as seen in conventional serum protein electrophoresis consists of 5 immunoglobulins. In normal serum, about 80% is immunoglobulin G (IgG). Elevations of IgG may be due to polyclonal immunoglobulin production. Monoclonal elevations of IgG characterize multiple myeloma. Monoclonal gammapathies of all types may lead to a spike in the gamma globulin zone seen on serum protein electrophoresis. Decreased immunoglobulin levels are found in patients with congenital deficiencies.

**Useful For:** Detecting or monitoring of monoclonal gammapathies and immune deficiencies

**Interpretation:** Increased serum immunoglobulin concentrations occur due to polyclonal or oligoclonal immunoglobulin proliferation in hepatic disease (hepatitis, liver cirrhosis), connective tissue diseases, acute and chronic infections, as well as in the cord blood of neonates with intrauterine and perinatal infections. Elevation of immunoglobulin G may occur in monoclonal gammapathies such as multiple myeloma, primary systemic amyloidosis, monoclonal gammapathy of undetermined significance, and related disorders. Decreased levels are found in patients with primary or secondary immune deficiencies.

**Reference Values:**

- 0-<5 months: 100-334 mg/dL
- 5-<9 months: 164-588 mg/dL
- 9-<15 months: 246-904 mg/dL
- 15-<24 months: 313-1,170 mg/dL
- 2-<4 years: 295-1,156 mg/dL
- 4-<7 years: 386-1,470 mg/dL
- 7-<10 years: 462-1,682 mg/dL
- 10-<13 years: 503-1,719 mg/dL
- 13-<16 years: 509-1,580 mg/dL
- 16-<18 years: 487-1,327 mg/dL
- > or =18 years: 767-1,590 mg/dL

**Clinical References:**

Immunoglobulin Gene Rearrangement, Blood

Clinical Information: The immunoglobulin (Ig) genes (heavy, kappa, and lambda) are comprised of numerous, discontinuous coding segments. As B cells develop, the segments are rearranged such that each mature B cell and plasma cell has a unique rearrangement profile. Other cell types usually retain the nonrearranged gene structures. Clonal expansion of any B cell or plasma cell will result in a population of cells that all contain an identical Ig gene rearrangement profile. Reactive B cell or plasma cell expansions are polyclonal, with each clone containing relatively few cells and no 1 clone predominating. Conversely, neoplastic clones are generally large such that the clonal cells are the predominant B cells or plasma cells present. In the appropriate clinical and pathologic setting, detection of a prominent Ig gene rearrangement profile may be equated to the presence of a neoplastic B-cell or plasma cell clone.

Useful For: Determining whether a B-cell or plasma cell population is polyclonal or monoclonal in peripheral blood specimens Identifying neoplastic cells as having B-cell or plasma cell differentiation Monitoring for a persistent neoplasm by detecting an immunoglobulin gene rearrangement profile similar to one from a previous neoplastic specimen

Interpretation: An interpretive report will be provided. The interpretation of the presence or absence of a predominant immunoglobulin (Ig) gene rearrangement profile is sometimes subjective. These results must always be interpreted in the context of other clinicopathologic information to determine the significance of the result. The detection of a clonal Ig gene rearrangement by this test is not synonymous with the presence of a B-cell or plasma cell neoplasm.

Reference Values: An interpretive report will be provided.


Immunoglobulin Gene Rearrangement, Bone Marrow

Clinical Information: The immunoglobulin (Ig) genes (heavy, kappa, and lambda) are comprised of numerous, discontinuous coding segments. As B-cells develop, the segments are rearranged such that each mature B-cell and plasma cell has a unique rearrangement profile. Other cell types usually retain the nonrearranged gene structures. Clonal expansion of any B-cell or plasma cell will result in a population of cells that all contain an identical Ig gene rearrangement profile. Reactive B-cell or plasma cell expansions are polyclonal, with each clone containing relatively few cells and no single clone predominating. Conversely, neoplastic clones are generally large such that the clonal cells are the predominant B-cells or plasma cells present. In the appropriate clinical and pathologic setting, detection of a prominent Ig gene rearrangement profile may be equated to the presence of a neoplastic B-cell or plasma cell clone.

Useful For: Determining whether a B-cell or plasma cell population is polyclonal or monoclonal in bone marrow specimens Identifying neoplastic cells as having B-cell or plasma cell differentiation Monitoring for a persistent neoplasm by detecting an immunoglobulin gene rearrangement profile similar to a previous neoplastic specimen

Interpretation: An interpretive report will be provided. The interpretation of the presence or absence of a predominant immunoglobulin (Ig) gene rearrangement profile is sometimes subjective. These results must always be interpreted in the context of other clinicopathologic information to determine the significance of the result. The detection of a clonal Ig gene rearrangement by this test is not synonymous with the presence of a B-cell or plasma cell neoplasm.
**Reference Values:**
An interpretive report will be provided.


### Immunoglobulin Gene Rearrangement, Varies

**Clinical Information:** The immunoglobulin (Ig) genes (heavy, kappa, and lambda) are comprised of numerous, discontinuous coding segments. As B cells develop, the segments are rearranged such that each mature B cell and plasma cell has a unique rearrangement profile. Other cell types usually retain the nonrearranged gene structures. Clonal expansion of any B cell or plasma cell will result in a population of cells that all contain an identical Ig gene rearrangement profile. Reactive B-cell or plasma cell expansions are polyclonal, with each clone containing relatively few cells and no single clone predominating. Conversely, neoplastic clones are generally large such that the clonal cells are the predominant B cells or plasma cells present. In the appropriate clinical and pathologic setting, detection of a prominent Ig gene rearrangement profile may be equated to the presence of a neoplastic B-cell or plasma cell clone.

**Useful For:** Determining whether a B-cell or plasma cell population is polyclonal or monoclonal in specimens other than blood or bone marrow Identifying neoplastic cells as having B-cell or plasma cell differentiation Monitoring for a persistent neoplasm by detecting an immunoglobulin gene rearrangement profile similar to that from a previous neoplastic specimen

**Interpretation:** An interpretive report will be provided. The interpretation of the presence or absence of a predominant immunoglobulin (Ig) gene rearrangement profile is sometimes subjective. These results must always be interpreted in the context of other clinicopathologic information to determine the significance of the result. The detection of a clonal Ig gene rearrangement by this test is not synonymous with the presence of a B-cell or plasma cell neoplasm.

**Reference Values:**
An interpretive report will be provided.


### Immunoglobulin Heavy and Light Chain (HLC) Pairs, IgA Kappa and IgA Lambda

**Clinical Information:** Plasma cell proliferative diseases such as multiple myeloma are defined by the monoclonal expansion of bone marrow plasma cells. The abnormal proliferation of clonal cells in the bone marrow can be identified by a skewed ratio of cells synthesizing kappa or lambda immunoglobulin. In addition, the secreted monoclonal immunoglobulin can usually be identified in serum or urine by protein electrophoresis and immunofixation electrophoresis. These electrophoretic procedures can show restricted immunoglobulin migration, characterize the heavy and/or light chains, and quantitate the monoclonal protein. Some monoclonal proteins, however, are difficult to identify and quantitate by electrophoretic assays. The serum concentration of monoclonal free light chains for example may not be high enough to be recognized or quantitated. Immunoassays that are specific for free light chains, as opposed to light chains bound to heavy chains, can quantitate kappa and lambda free light chains. An abnormal ratio of the free light chains can identify excess clonal plasma cell proliferation and the concentration of the monoclonal free light chain can be determined. Another
example of proteins that are difficult to identify and quantitate are monoclonal proteins that are intact immunoglobulins (heavy and light chains) that migrate very broadly in the gamma fraction or migrate within the beta or alpha fractions. Immunoassays that are specific for heavy and light chain pairs (HLC) such as IgA kappa or IgA lambda can quantitate the individual HLC pairs and be used to identify abnormal ratios of the HLC pairs and to quantitate the monoclonal HLC pair.

**Useful For:** The quantitation of heavy and light chain pairs is useful for: 1. Distinguishing between broadly migrating monoclonal proteins and restricted polyclonal immunoglobulin responses 2. Quantitating monoclonal IgA proteins that are difficult to quantitate on serum protein electrophoresis 3. Providing a more specific quantitation of the monoclonal protein than quantitating total IgA

**Interpretation:** An elevated IgA heavy and light chain (HLC) pairs ratio suggests a clonal proliferation of an IgA kappa clone of plasma cells. A low IgA HLC pair ratio suggests a clonal proliferation of an IgA lambda clone of plasma cells.

**Reference Values:**
Total IgA
- 0-<5 months: 7-37 mg/dL
- 5-<9 months: 16-50 mg/dL
- 9-<15 months: 27-66 mg/dL
- 15-<24 months: 36-79 mg/dL
- 2-<4 years: 27-246 mg/dL
- 4-<7 years: 29-256 mg/dL
- 7-<10 years: 34-274 mg/dL
- 10-<13 years: 42-295 mg/dL
- 13-<16 years: 52-319 mg/dL
- 16-<18 years: 60-337 mg/dL
- > or =18 years: 61-356 mg/dL

- IgA kappa: 53-262 mg/dL
- IgA lambda: 38-181 mg/dL
- AK/AL ratio: 0.5300-2.52

**Clinical References:**

**Immunoglobulin Heavy and Light Chain (HLC) Pairs, IgG Kappa and IgG Lambda**

**Clinical Information:** Plasma cell proliferative diseases such as multiple myeloma are defined by the monoclonal expansion of bone marrow plasma cells. The abnormal proliferation of clonal cells in the bone marrow can be identified by a skewed ratio of cells synthesizing kappa or lambda immunoglobulin. In addition, the secreted monoclonal immunoglobulin can usually be identified in serum or urine by protein electrophoresis and immunofixation electrophoresis. These electrophoretic procedures can show restricted immunoglobulin migration, characterize the heavy and/or light chains, and quantitate the monoclonal protein. Some monoclonal proteins, however, are difficult to identify and quantitate by electrophoretic assays. The serum concentration of monoclonal free light chains for example may not be high enough to be recognized or quantitated. Immunoassays that are specific for free light chains, as opposed to light chains bound to heavy chains, can quantitate kappa and lambda free light chains. An abnormal ratio of the free light chains can identify excess clonal plasma cell proliferation and the concentration of the monoclonal free light chain can be determined. Another example of proteins that are difficult to identify and quantitate are monoclonal proteins that are intact immunoglobulins (heavy and light chains) that migrate very broadly in the gamma fraction or migrate within the beta or alpha fractions. Immunoassays that are specific for heavy and light chain pairs (HLC) such as IgG kappa or IgG lambda.
can quantitate the individual HLC pairs and be used to identify abnormal ratios of the HLC pairs and to
quantitate the monoclonal HLC pair.

**Useful For:** The quantitation of heavy and light chain pairs is useful for: 1. Distinguishing between
broadly migrating monoclonal proteins and restricted polyclonal immunoglobulin responses 2.
Quantitating monoclonal IgG proteins that are difficult to quantitate on serum protein electrophoresis 3.
Providing a more specific quantitation of the monoclonal protein than quantitating total IgG

**Interpretation:** An elevated IgG heavy and light chain (HLC) pair ratio suggests a clonal
proliferation of an IgG kappa clone of plasma cells. A low IgG HLC pair ratio suggests a clonal
proliferation of an IgG lambda clone of plasma cells.

**Reference Values:**

- **Total IgG**
  - 0-<5 months: 100-334 mg/dL
  - 5-<9 months: 164-588 mg/dL
  - 9-<15 months: 246-904 mg/dL
  - 15-<24 months: 313-1,170 mg/dL
  - 2-<4 years: 295-1,156 mg/dL
  - 4-<7 years: 386-1,470 mg/dL
  - 7-<10 years: 462-1,682 mg/dL
  - 10-<13 years: 503-1,719 mg/dL
  - 13-<16 years: 509-1,580 mg/dL
  - 16-<18 years: 487-1,327 mg/dL
  - > or =18 years: 767-1,590 mg/dL

- **IgG kappa**: 434-1080 mg/dL
- **IgG lambda**: 177-531 mg/dL
- **GK/GL ratio**: 1.06-4.46

**Clinical References:** 1. Donato LJ, Zeldenrust SR, Murray DL, Katzmann JA: A 71-year-old
woman with multiple myeloma status after stem cell transplantation. Clin Chem 2011
gammopathies by nephelometric measurement of individual immunoglobulin kappa/lambda ratios. Clin
Chem 2009 Sept;55(9):1646-1655
broadly migrating monoclonal proteins and restricted polyclonal immunoglobulin responses. Quantitating monoclonal IgM proteins that are difficult to quantitate on serum protein electrophoresis. Providing a more specific quantitation of the monoclonal protein than quantitating total IgM.

**Interpretation:** An elevated IgM heavy and light chain (HLC) pair ratio suggests a clonal proliferation of an IgM kappa clone of plasma cells. A low IgM HLC pair ratio suggests a clonal proliferation of an IgM lambda clone of plasma cells.

**Reference Values:**

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<th>Age Range</th>
<th>Total IgM</th>
<th>IgM kappa</th>
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<td>5-&lt;9 months</td>
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<td>2-&lt;4 years</td>
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**Clinical References:**

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**Immunoglobulin M (IgM), Serum**

**Clinical Information:** The gamma-globulin band as seen in conventional serum protein electrophoresis consists of 5 immunoglobulins. In normal serum, about 5% is immunoglobulin M (IgM). Elevations of IgM may be due to polyclonal immunoglobulin production. Monoclonal elevations of IgM occur in macroglobulinemia. Monoclonal gammopathies of all types may lead to a spike in the gamma-globulin zone seen on serum protein electrophoresis. Decreased immunoglobulin levels are found in patients with congenital deficiencies.

**Useful For:** Detecting or monitoring of monoclonal gammopathies and immune deficiencies

**Interpretation:** Increased serum immunoglobulin concentrations occur due to polyclonal or oligoclonal immunoglobulin proliferation in hepatic disease (hepatitis, liver cirrhosis), connective tissue diseases, acute and chronic infections, as well as in the cord blood of neonates with intrauterine and perinatal infections. Elevation of immunoglobulin M may occur in monoclonal gammopathies such as macroglobulinemia, primary systemic amyloidosis, monoclonal gammopathy of undetermined significance, and related disorders. Decreased levels are found in patients with primary or secondary immune deficiencies.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Total IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-&lt;5 months</td>
<td>26-122 mg/dL</td>
</tr>
<tr>
<td>5-&lt;9 months</td>
<td>32-132 mg/dL</td>
</tr>
<tr>
<td>9-&lt;15 months</td>
<td>40-143 mg/dL</td>
</tr>
<tr>
<td>15-&lt;24 months</td>
<td>46-152 mg/dL</td>
</tr>
<tr>
<td>2-&lt;4 years</td>
<td>37-184 mg/dL</td>
</tr>
<tr>
<td>4-&lt;7 years</td>
<td>37-224 mg/dL</td>
</tr>
</tbody>
</table>
Immunoglobulin Subclass IgG4, Serum

Clinical Information: The most abundant immunoglobulin isotype in human serum is immunoglobulin G (IgG). IgG immunoglobulins are comprised of 4 subclasses designated IgG1 through IgG4. Of total IgG, approximately 65% is IgG1, 25% is IgG2, 6% is IgG3, and 4% is IgG4. Each IgG subclass contains structurally unique portions of the constant region of the gamma heavy chain. IgG subclass 4-related disease is a recently recognized syndrome of unknown etiology most often occurring in middle-aged and older men. Several organ systems can be involved and encompasses many previous and newly described diseases such as type I autoimmune pancreatitis; Mikulicz disease and sclerosing sialadenitis; inflammatory orbital pseudotumor; chronic sclerosing aortitis; Riedel thyroiditis, a subset of Hashimoto thyroiditis; IgG4-related interstitial pneumonitis; and IgG4-related tubulointerstitial nephritis. Each of these entities is characterized by tumor-like swelling of the involved organs with infiltrative, predominately IgG4-positive, plasma cells with accompanying "storiform" fibrosis. In addition, elevated serum concentrations of IgG4 are found in 60% to 70% of patients diagnosed with IgG4-related disease. The diagnosis of IgG4-related disease requires a tissue biopsy of the affected organ demonstrating the aforementioned histological features. It is recommended that patients suspected of having an IgG4-related disease have their serum IgG4 level measured.

Useful For: Supporting the diagnosis of IgG4-related disease

Interpretation: Elevated levels of IgG4 are consistent with, but not diagnostic of, IgG4-related disease.

Reference Values:
0-<5 months: < or =19.8 mg/dL
5-<9 months: < or =20.8 mg/dL
9-<15 months: < or =22.0 mg/dL
15-<24 months: < or =23.0 mg/dL
2-<4 years: 0.4-49.1 mg/dL
4-<7 years: 0.8-81.9 mg/dL
7-<10 years: 1.0-108.7 mg/dL
10-<13 years: 1.0-121.9 mg/dL
13-<16 years: 0.7-121.7 mg/dL
16-<18 years: 0.3-111.0 mg/dL
> or =18 years: 2.4-121.0 mg/dL


**Immunoglobulin Total Light Chains, Urine**

**Clinical Information:** Immunoglobulin light chains are usually cleared from blood through the renal glomeruli and reabsorbed in the proximal tubules so that urine light-chain concentrations are very low or undetectable. The production of large amounts of monoclonal light chains, however, can overwhelm this reabsorption mechanism. The detection of monoclonal light chains in the urine (Bence Jones proteinuria) has been used as a diagnostic marker for multiple myeloma since the report by Dr. H. Bence Jones in 1847. Current laboratory procedures employ protein electrophoresis and immunofixation for the identification and characterization of urine monoclonal light chains, and the monoclonal light chains may be present in large enough amounts to also be quantitated as an M-spike on protein electrophoresis. The electrophoretic M-spike is the recommended method of monitoring monoclonal gammopathies such as multiple myeloma. Monitoring the urine M-spike is especially useful in patients with light-chain multiple myeloma in whom the serum M-spike is very small or absent, but the urine M-spike is large. Just as quantitative serum immunoglobulins by immunonephelometry are a complement to M-spike quantitation by serum electrophoresis, this quantitative urine light-chain assay may be used to complement urine M-spike quantitation by electrophoresis.

**Useful For:**
- Monitoring patients whose urines demonstrate large M-spikes
- Confirming the quantitation of specimens that show M-spikes by electrophoresis
- Detecting urine monoclonal proteins and identification of specimens that need urine protein electrophoresis

**Interpretation:**
A kappa/lambda (K/L) ratio >6.2 suggests the presence of monoclonal kappa light chains. A K/L ratio <0.7 suggests the presence of monoclonal lambda light chains. In 24-hour specimens, a >90% increase in concentration suggests progression or relapse; a >90% decrease suggests treatment response. Increased kappa and/or lambda light chains may be seen in benign (polyclonal) and neoplastic (monoclonal) disorders.

**Reference Values:**
- **KAPPA TOTAL LIGHT CHAIN**
  - <0.9 mg/dL
- **LAMBDA TOTAL LIGHT CHAIN**
  - <0.7 mg/dL
- **KAPPA/LAMBDA RATIO**
  - 0.7-6.2

**Clinical References:**

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**Immunoglobulins (IgG, IgA, and IgM), Serum**

**Clinical Information:** The gamma globulin band as seen in conventional serum protein electrophoresis consists of 5 immunoglobulins. In normal serum, about 80% is immunoglobulin G (IgG), 15% is immunoglobulin A (IgA), 5% is immunoglobulin M (IgM), 0.2% is immunoglobulin D (IgD), and a trace is immunoglobulin E (IgE). Elevations of IgG, IgA, and IgM may be due to polyclonal immunoglobulin production. Monoclonal gammopathies of all types may lead to a spike in the gamma globulin zone seen on serum protein electrophoresis. Monoclonal elevations of IgG, IgA, IgD, and IgE characterize multiple myeloma. Monoclonal elevations of IgM occur in macroglobulinemia. Decreased immunoglobulin levels are found in patients with congenital deficiencies.

**Useful For:** Detecting or monitoring of monoclonal gammopathies and immune deficiencies

Current as of October 11, 2018 2:20 pm CDT
**Interpretation:** Increased serum immunoglobulin concentrations occur due to polyclonal or oligoclonal immunoglobulin proliferation in hepatic disease (hepatitis, liver cirrhosis), connective tissue diseases, acute and chronic infections, as well as in the cord blood of neonates with intrauterine and perinatal infections. Elevations of immunoglobulin G (IgG), immunoglobulin A (IgA), or immunoglobulin M (IgM) may occur in monoclonal gammopathies such as multiple myeloma (IgG, IgA), macroglobulinemia (IgM), primary systemic amyloidosis, monoclonal gammopathy of undetermined significance, and related disorders. Decreased levels are found in patients with primary or secondary immune deficiencies.

**Reference Values:**

**IgG**
- 0-<5 months: 100-334 mg/dL
- 5-<9 months: 164-588 mg/dL
- 9-<15 months: 246-904 mg/dL
- 15-<24 months: 313-1,170 mg/dL
- 2-<4 years: 295-1,156 mg/dL
- 4-<7 years: 386-1,470 mg/dL
- 7-<10 years: 462-1,682 mg/dL
- 10-<13 years: 503-1,719 mg/dL
- 13-<16 years: 509-1,580 mg/dL
- 16-<18 years: 487-1,327 mg/dL
- > or =18 years: 767-1,590 mg/dL

**IgA**
- 0-<5 months: 7-37 mg/dL
- 5-<9 months: 16-50 mg/dL
- 9-<15 months: 27-66 mg/dL
- 15-<24 months: 36-79 mg/dL
- 2-<4 years: 27-246 mg/dL
- 4-<7 years: 29-256 mg/dL
- 7-<10 years: 34-274 mg/dL
- 10-<13 years: 42-295 mg/dL
- 13-<16 years: 52-319 mg/dL
- 16-<18 years: 60-337 mg/dL
- > or =18 years: 61-356 mg/dL

**IgM**
- 0-<5 months: 26-122 mg/dL
- 5-<9 months: 32-132 mg/dL
- 9-<15 months: 40-143 mg/dL
- 15-<24 months: 46-152 mg/dL
- 2-<4 years: 37-184 mg/dL
- 4-<7 years: 37-224 mg/dL
- 7-<10 years: 38-251 mg/dL
- 10-<13 years: 41-255 mg/dL
- 13-<16 years: 45-244 mg/dL
- 16-<18 years: 49-201 mg/dL
- > or =18 years: 37-286 mg/dL

**Clinical References:**
Immunoglobulins, CSF Quantitative

Reference Values:
- Immunoglobulin M CSF (0.0 - 0.7) mg/dL
- Immunoglobulin G CSF (0.0 - 6.0) mg/dL
- Immunoglobulin A CSF (0.0 - 0.7) mg/dL

Infectious Mononucleosis, Rapid Test, Serum

Clinical Information: Infectious mononucleosis (IM) is a viral illness that involves reticuloendothelial tissue and is generally limited to children and young adults. IM is most commonly caused by Epstein-Barr virus (EBV). The disease is characterized by fever, sore throat, lymphadenopathy, headache, and fatigue, and on a symptomatic basis may be confused with other diseases. Detectable levels of unique heterophile antibodies are produced in patients with IM.

Useful For: Rapid confirmation of a diagnosis of infectious mononucleosis

Interpretation: Detectable levels of the infectious mononucleosis (IM) heterophile antibody can usually be expected to occur between the sixth and tenth day following the onset of symptoms. The level usually increases through the second or third week of illness and, thereafter, can be expected to persist, gradually declining over a 12-month period.

Reference Values:
Negative
Reference values apply to all ages.


Inflammatory Bowel Disease Primary Immunodeficiency (PID) Panel

Clinical Information: Patients with a diverse spectrum of rare genetic disorders can present with inflammatory bowel disease (IBD). Patients with these disorders often develop symptoms during infancy or early childhood, along with endoscopic and histological features of Crohn disease, ulcerative colitis (UC), or unclassified forms of IBD. Excessive and chronic bowel inflammation may occur as a reaction to normal gastrointestinal flora in genetically susceptible individuals. About half of the risk of developing Crohn disease is genetically determined, while the remaining risk is modulated by environmental factors including diet and cigarette smoking. Inflammatory bowel disorders affect approximately 1 in 250 people in Western Europe, North America, and Australasia. The incidence is increasing in the developing world. Crohn disease can affect any part of the bowel, from the mouth to the anus with inflammatory disease frequently progressing to cause strictures and fistulae in the bowel. The usual age of onset is between 15 and 30 years, but the disease can occur at any age. UC is restricted to the colon, but has 2 important consequences: severe attacks with a high risk of urgent surgery, and an increased risk of bowel cancer. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome shares some common features with IBD. Diagnosis is based on clinical features and genetic testing. Patients with features of humoral immunodeficiency may also develop enteropathy and features of IBD, for example with lipopolysaccharide (LPS)-responsive and beige-like anchor protein (LRBA) deficiency. There are several monogenic disorders that can present with an IBD-like pathology. The prevalence of these monogenic diseases is relatively low compared to more intestinal diseases, including infections, celiac
disease, and IBD. However, since the monogenic disorders are associated with high morbidity and mortality, it is imperative to diagnose them early. IBD developing in the neonatal or infantile periods is classified as very early-onset IBD (VEOIBD) and accounts for less than 1% of pediatric patients. However, the clinical course is very severe and there is a high rate of resistance to immunosuppressive treatment. Table 1. Genes included in the Inflammatory Bowel Disease/Enteropathy/Hepatic PID Panel

<table>
<thead>
<tr>
<th>GENE SYMBOL (ALIAS)</th>
<th>PROTEIN</th>
<th>OMIM</th>
<th>INCIDENCE</th>
<th>INHERITANCE</th>
<th>PHENOTYPE</th>
<th>DISORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOXP3</td>
<td>Forkhead box protein P3 isoform a</td>
<td>300292</td>
<td>Rare</td>
<td>XL</td>
<td>X-linked immunodysregulation, polyendocrinopathy, and enteropathy (IPEX)</td>
<td></td>
</tr>
<tr>
<td>IL10</td>
<td>Interleukin-10 precursor</td>
<td>124092</td>
<td>AR</td>
<td>Inflammatory bowel disease, folliculitis, recurrent respiratory diseases, arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL10RA</td>
<td>Interleukin-10 receptor subunit alpha precursor</td>
<td>146933</td>
<td>AR</td>
<td>Inflammatory bowel disease 28, early onset; folliculitis, recurrent respiratory diseases, arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL10RB</td>
<td>Interleukin-10 receptor subunit beta precursor</td>
<td>123889</td>
<td>AR</td>
<td>Inflammatory bowel disease 25, early onset; folliculitis, recurrent respiratory diseases, arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL21</td>
<td>Interleukin-21 isoform 1 precursor</td>
<td>605384</td>
<td>AR</td>
<td>Immunodeficiency, common variable, 11; severe early onset colitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL21R</td>
<td>Interleukin-21 receptor isoform 1 precursor</td>
<td>605383</td>
<td>AR/AD</td>
<td>Immunodeficiency, susceptibility to cryptosporidia and pneumocystis, susceptibility to cholangitis (AR); elevated IgE (AD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITCH</td>
<td>E3 ubiquitin-protein ligase itchy homolog isoform 2</td>
<td>606409</td>
<td>AR</td>
<td>Early onset chronic lung disease (interstitial pneumonitis), autoimmune disorders (thyroiditis, type 1 diabetes, chronic diarrhea/enteropathy, and hepatitis), with facial dysmorphism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LRBA</td>
<td>Lipopolysaccharide-responsive and beige-like anchor protein isoform 2</td>
<td>606453</td>
<td>Unknown</td>
<td>AR</td>
<td>Common variable immunodeficiency (CVID) 8 with autoimmunity, inflammatory bowel disease</td>
<td></td>
</tr>
<tr>
<td>NOD2</td>
<td>Nucleotide-binding oligomerization domain-containing protein 2 isoform 1</td>
<td>605956</td>
<td>AD</td>
<td>Blau syndrome, early-onset sarcoidosis, Inflammatory bowel disease 1, susceptibility to psoriatic arthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAT3 (Gain-of function)</td>
<td>Signal transducer and activator of transcription 3 isoform 1</td>
<td>102582</td>
<td>Approximately 40%</td>
<td>HIES AD</td>
<td>Autoimmune disease, multisystem, infantile-onset, enteropathy, IBD</td>
<td></td>
</tr>
<tr>
<td>STAT5B</td>
<td>Signal transducer and activator of transcription 5B</td>
<td>604260</td>
<td>Rare</td>
<td>AR</td>
<td>Growth hormone insensitivity with immunodeficiency</td>
<td></td>
</tr>
<tr>
<td>TTC37</td>
<td>Tetratricopeptide repeat protein 37</td>
<td>614589</td>
<td>Unknown</td>
<td>AR</td>
<td>Early-onset sarcoidosis, inflammatory bowel disease 1, susceptibility to psoriatic arthritis</td>
<td></td>
</tr>
<tr>
<td>TTC7A</td>
<td>Tetratricopeptide repeat protein 7A isoform 2</td>
<td>609332</td>
<td>AR</td>
<td>Immunodeficiency with multiple intestinal atresias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XIAP</td>
<td>E3 ubiquitin-protein ligase</td>
<td>300079</td>
<td>1/million males</td>
<td>XL</td>
<td>X-linked lymphoproliferative syndrome, colitis, IBD, hepatitis</td>
<td></td>
</tr>
</tbody>
</table>

**Useful For:**
Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of inflammatory bowel disease (IBD), enteropathy, hepatic primary immunodeficiency (PID), or intestinal manifestation associated with immunodeficiency. Establishing a diagnosis and, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved. Identifying variants within genes known to be associated with IBD, enteropathy, hepatic PID, or related disorders allowing for predictive testing of at-risk family members.

**Interpretation:**
Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
5. Flangan SE, Haapaniemi E, Russell MA, et al:

**Inflammatory Bowel Disease Serology Panel, Serum**

**Clinical Information:** The term "inflammatory bowel disease" (IBD) is often used to refer to 2 diseases, ulcerative colitis (UC) and Crohn's disease (CD), that produce inflammation of the large or small intestines. The diagnosis of these 2 diseases is based on clinical features, the results of barium X-rays, colonoscopy, mucosal biopsy histology, and in some cases operative findings and resected bowel pathology and histology. Recently, patients with IBD have been shown to have antibodies in serum that help to distinguish between CD and UC.(1) Patients with UC often have measurable neutrophil specific antibodies (NSA), which react with as yet uncharacterized target antigens in human neutrophils; whereas, patients with CD often have measurable antibodies of the IgA and/or IgG isotypes, which react with cell wall mannan of Saccharomyces cerevisiae strain Su 1.

**Useful For:** As an adjunct in the diagnosis of ulcerative colitis and Crohn's disease in patients suspected of having inflammatory bowel disease

**Interpretation:** The finding of neutrophil specific antibodies (NSA) with normal levels of IgA and IgG anti-Saccharomyces cerevisiae antibodies (ASCA) is consistent with the diagnosis of ulcerative colitis (UC); the finding of negative NSA with elevated IgA and IgG ASCA is consistent with Crohn's disease (CD). NSA are detectable in approximately 50% of patients with UC, and elevated levels of either IgA or IgG ASCA occur in approximately 55% of patients with CD. Approximately 40% of patients with CD have elevated levels of both IgA and IgG ASCA. Employed together, the tests for NSA and ASCA have the following positive predictive values (PV) for UC and CD, respectively: NSA positive with normal levels of IgA and IgG ASCA, PV of 91%; NSA negative with elevated levels if IgA and IgG ASCA, PV of 90%.(2)

**Reference Values:**
Saccharomyces cerevisiae ANTIBODY, IgA  
Negative: < or =20.0 U  
Equivocal: 20.1-24.9 U  
Weakly positive: 25.0-34.9 U  
Positive: > or =35.0 U  

Saccharomyces cerevisiae ANTIBODY, IgG  
Negative: < or =20.0 U  
Equivocal: 20.1-24.9 U  
Weakly positive: 25.0-34.9 U  
Positive: > or =35.0 U  

NEUTROPHIL-SPECIFIC ANTIBODIES  
Negative (not detectable)

**Clinical Information:** Inflammatory myofibroblastic tumor (IMT) is a distinctive lesion composed of myofibroblastic spindle cells accompanied by an inflammatory infiltrate of plasma cells, lymphocytes, and eosinophils which occur primarily in the soft tissue and viscera of children and young adults. They may arise in any anatomical site including lung, soft tissue, retroperitoneum, and bladder. The genetic mechanisms underlying IMT pathogenesis are only partially known, but cytogenetic analyses have disclosed chromosomal rearrangements involving the ALK gene at 2p23. Studies support that identification of ALK gene rearrangement is useful to differentiate IMTs from other spindle cell neoplasms of soft tissue and viscera.

**Useful For:** Supporting the diagnosis of inflammatory myofibroblastic tumor when used in conjunction with an anatomic pathology consultation

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the ALK probe set. A positive result is consistent with a subset of inflammatory myofibroblastic tumor (IMT). A negative result suggests that an ALK gene rearrangement is not present but does not exclude the diagnosis of IMT.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

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**Infliximab Quantitation with Reflex to Antibodies to Infliximab, Serum**

**Clinical Information:** Infliximab (Remicade, Janssen Biotech) is a chimeric immunoglobulin (IgG1 kappa) targeting tumor necrosis factor-alpha (TNF-a), and is currently FDA-approved for the treatment of multiple inflammatory conditions. Infliximab binds to soluble TNF-a and transmembrane homotrimers. Infliximab pharmacokinetic properties may vary with disease and clearance is affected by concomitant use of immunosuppressants, high concentrations of TNF-a and C-reactive proteins,(1,2) low albumin concentrations, high body mass index, and presence of antibodies to infliximab, also known as human antichimeric antibodies (HACA).(3) Males seem to clear infliximab faster than females.(3) Several studies have demonstrated that infliximab quantitation in the setting of loss of response to therapy can aid in patient management, as trough concentrations defined as therapeutic have been associated with superior clinical response and improved prognosis.(4-6) Evaluation of infliximab concentrations may be of value for all inflammatory diseases for which it is prescribed. Primary indications for testing of infliximab include loss of response, partial response on initiation of therapy, autoimmune or hypersensitivity reactions, primary nonresponse, reintroduction after drug holiday, endoscopic/computed tomography enterography recurrence (in inflammatory bowel disease), and acute infusion reactions. Measurement of infliximab concentrations is indicated at trough, immediately prior to the next scheduled infusion. Low trough concentrations may be correlated with loss of response to infliximab. Assessment of antibodies to infliximab is suggested when infliximab quantitation at trough is less than or equal to 5.0 mcg/mL. The infliximab assay has been verified to analyze infliximab and infliximab-dyyb (Inflectra, Pfizer Inc) with no analytical differences between the 2 drugs quantitation. Inflectra has the same primary amino acid sequence as Remicade. Inflectra was approved by the FDA for use in April 2016 and became available in December 2016 in the US market. Therefore, â€œinfliximabâ€• will be used to refer to both the reference product and the biosimilar interchangeably.
A biosimilar product is a biological product that is approved based on showing that it is highly similar to an FDA-approved biological product, known as the reference product. No clinically meaningful differences in terms of safety and effectiveness from the reference product are present. Only minor differences in clinically inactive components are allowable in biosimilar products. In contrast to generic medications, a prescription of biosimilars needs to come from the ordering physician and not the dispensing pharmacy (pharmacies cannot substitute a biosimilar for another medication; a separate prescription is required).

**Useful For:** Trough level quantitation for evaluation of patients with loss of response to infliximab and infliximab-dyyb

**Interpretation:** Low trough concentrations may be correlated with loss of response to infliximab. For infliximab trough concentrations less than or equal to 5.0 mcg/mL, testing for antibodies to infliximab (ATI) is suggested. For infliximab trough concentrations above 5.0 mcg/mL, the presence of ATI is unlikely; patients experiencing loss of response to infliximab may benefit from an increased dose or a shorter infusion interval. Results above 35 mcg/mL are suggestive of a blood draw at a time-point in treatment other than trough.

**Reference Values:**
Limit of quantitation is 1.0 mcg/mL. Therapeutic ranges are disease specific.

Pediatric reference ranges are not established.

**Clinical References:**

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**Influenza Virus A Antibodies, IgG and IgM (Separate Determinations), Serum**

**Clinical Information:** Influenza is usually a mild illness of the upper respiratory tract. Involvement of the lower respiratory tract, however, can lead to 4 types of clinical syndromes: physical signs of lower respiratory tract involvement without roentgenographic evidence of pneumonia, influenza complicated by bacterial pneumonia, primary influenza virus pneumonia, and combined influenzal and bacterial pneumonias. Incidence of influenza virus infections is seasonal in the United States and usually occurs only from November to March. Influenza virus infections are most severe in patients with certain preexisting conditions such as rheumatic heart disease, bronchopulmonary disease, impaired renal function, and diabetes mellitus. Infections can be more severe in elderly patients, pregnant females, and immunocompromised patients. Influenza virus type A can produce serious illness during the first 2 years of life, with croup, bronchitis, and pneumonia being prominent. Influenza A may also precipitate asthmatic attacks and produce chronic pulmonary complications in children.

**Useful For:** Diagnosis of recent infection by influenza virus type A when isolation of the organism by culture is unsuccessful

**Interpretation:** The presence of IgM class antibody or a 4-fold or greater rise in titer in paired (acute and convalescent) sera indicates recent infection. The presence of IgG class antibody generally indicates past exposure.
Influenza Virus B Antibodies, IgG and IgM (Separate Determinations), Serum

**Clinical Information:** Influenza is usually a mild illness of the upper respiratory tract. Involvement of the lower respiratory tract, however, can lead to 4 types of clinical syndromes: physical signs of lower respiratory tract involvement without roentgenographic evidence of pneumonia, influenza complicated by bacterial pneumonia, primary influenza virus pneumonia, and combined influenza and bacterial pneumonias. Incidence of influenza virus infections is seasonal in the United States and usually occurs only from November to March. Influenza virus infections are most severe in patients with certain preexisting conditions such as rheumatic heart disease, bronchopulmonary disease, impaired renal function, and diabetes mellitus. Infections can be more severe in elderly patients, pregnant females, and immunocompromised patients. Influenza virus type B generally produces less severe disease than type A. Outbreaks of influenza type B virus are usually more localized than type A. Both infections occur in the United States between November and March. Influenza A is susceptible to antiviral activity of amantadine while influenza B is not inhibited by this drug.

**Useful For:** Diagnosis of recent infection by influenza virus type B when isolation of the organism by culture is unsuccessful

**Interpretation:** The presence of IgM class antibody or a 4-fold or greater rise in titer in paired (acute and convalescent) sera indicates recent infection. The presence of IgG class antibody alone generally indicates past exposure.

**Reference Values:**
- IgG: <1:10
- IgM: <1:10
  
Reference values apply to all ages.

**Clinical References:**

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Influenza Virus Type A and Type B, and Respiratory Syncytial Virus (RSV), Molecular Detection, PCR, Miscellaneous Sources

**Clinical Information:** Influenza, otherwise known as the "flu," is an acute, contagious respiratory illness caused by influenza A, B, and C viruses. Of these, only influenza A and B are thought to cause significant disease, with infections due to influenza B usually being milder than infections with influenza A. Influenza A viruses are further categorized into subtypes based on the 2 major surface protein antigens: hemagglutinin (H) and neuraminidase (N). Common symptoms of influenza infection include fever, chills, sore throat, muscle pains, severe headache, weakness, fatigue, and a nonproductive cough. Certain patients, including infants, the elderly, the immunocompromised, and those with impaired lung function, are at risk for serious complications. In the United States, influenza results in approximately 36,000 deaths and more than 200,000 hospitalizations each year.(1) In the northern hemisphere, annual epidemics of influenza typically occur during the fall or winter months. However,
the peak of influenza activity can occur as late as April or May, and the timing and duration of flu seasons vary. In 2009 to 2010, a novel influenza virus (called 2009 H1N1, previously "swine" flu) appeared in Mexico and quickly spread worldwide, causing the first influenza pandemic in more than 40 years. The resultant influenza season had an atypical distribution, with illness occurring during normally low-incidence months. Following a pandemic, disease incidence usually returns to the typical seasonal distribution within 1 to 2 years.(1) Influenza infection may be treated with supportive therapy, as well as antiviral drugs such as the neuraminidase inhibitors, oseltamivir (TAMIFLU) and zanamivir (RELENZA). These drugs are most effective when given within the first 48 hours of infection, so prompt diagnosis and treatment are essential for proper management. Respiratory syncytial virus (RSV) is a respiratory virus that also infects the respiratory system and can cause an influenza-like illness. Most otherwise healthy people recover from RSV infection in 1 to 2 weeks. However, infection can be severe in infants, young children, and older adults. RSV is the most common cause of bronchiolitis (inflammation of the small airways in the lung) and pneumonia in children under 1 year of age in the United States, and is more frequently being recognized as an important cause of respiratory illness in older adults.(2) RSV and influenza virus RNA can be detected by PCR in respiratory secretions, including upper and lower respiratory specimens. Nasopharyngeal swabs or aspirates are the preferred specimen types for detection of RNA from influenza A, influenza B, and RSV. Nasal swabs have also been shown to provide equivalent yield to nasopharyngeal specimens for molecular detection of influenza A and B RNA, but not RSV RNA.(3,4) Tracheal aspirates are generally not acceptable for testing due to the viscous nature of these specimens.

**Useful For:** Rapid and accurate detection of influenza A, influenza B, and respiratory syncytial virus in a single test

**Interpretation:** A positive test result indicates that the patient is presumptively infected with the indicated virus. The test does not indicate the stage of infection. Rarely, more than 1 virus may be detected from the same patient specimen. Laboratory test results should always be considered in the context of clinical observations and epidemiologic data in making a final diagnosis. A negative test result suggests that the patient is not infected with influenza A, influenza B, or respiratory syncytial virus (RSV).

**Reference Values:**

**Clinical References:**

**Influenza Virus Type A and Type B, and Respiratory Syncytial Virus (RSV), Molecular Detection, PCR, Nasopharyngeal Swab**

**Clinical Information:** Influenza, otherwise known as the “flu,” is an acute, contagious respiratory illness caused by influenza A, B, and C viruses. Of these, only influenza A and B are thought to cause significant disease, with infections due to influenza B usually being milder than infections with influenza A. Influenza A viruses are further categorized into subtypes based on the 2 major surface protein antigens: hemagglutinin (H) and neuraminidase (N). Common symptoms of influenza infection include fever, chills, sore throat, muscle pains, severe headache, weakness, fatigue, and a nonproductive cough. Certain patients, including infants, the elderly, the immunocompromised, and those with impaired lung function, are at risk for serious complications. In the United States, influenza results in approximately 36,000 deaths and more than 200,000 hospitalizations each year.(1) In the northern hemisphere, annual epidemics of influenza typically occur during the fall or winter months. However, the peak of influenza activity can occur as late as April or May, and the timing and duration of flu seasons vary. In 2009 to 2010, a novel
influenza virus (called 2009 H1N1, previously "swine" flu) appeared in Mexico and quickly spread worldwide, causing the first influenza pandemic in more than 40 years. The resultant influenza season had an atypical distribution, with illness occurring during normally low-incidence months. Following a pandemic, disease incidence usually returns to the typical seasonal distribution within 1 to 2 years. Influenza infection may be treated with supportive therapy, as well as antiviral drugs such as the neuraminidase inhibitors, oseltamivir (TAMIFLU) and zanamivir (RELENZA). These drugs are most effective when given within the first 48 hours of infection, so prompt diagnosis and treatment are essential for proper management. Respiratory syncytial virus (RSV) is a respiratory virus that also infects the respiratory system and can cause an influenza-like illness. Most otherwise healthy people recover from RSV infection in 1 to 2 weeks. However, infection can be severe in infants, young children, and older adults. RSV is the most common cause of bronchiolitis (inflammation of the small airways in the lung) and pneumonia in children under 1 year of age in the United States, and is more frequently being recognized as an important cause of respiratory illness in older adults. RSV and influenza virus RNA can be detected by PCR in respiratory secretions, including upper and lower respiratory specimens. Nasopharyngeal swabs or aspirates are the preferred specimen types for detection of RNA from influenza A, influenza B, and RSV. Nasal swabs have also been shown to provide equivalent yield to nasopharyngeal specimens for molecular detection of influenza A and B RNA, but not RSV RNA. Nasopharyngeal aspirates are generally not acceptable for testing due to the viscous nature of these specimens. 

Useful For: Rapid and accurate detection of influenza A, influenza B, and respiratory syncytial virus in a single test for nasopharyngeal swab specimens

Interpretation: A positive test result indicates that the patient is presumptively infected with the indicated virus. The test does not indicate the stage of infection. Rarely, more than 1 virus may be detected from the same patient specimen. Laboratory test results should always be considered in the context of clinical observations and epidemiologic data in making a final diagnosis. A negative test result suggests that the patient is not infected with influenza A, influenza B, or respiratory syncytial virus (RSV).

Reference Values:


INHAB 86336

Inhibit A and B, Tumor Marker, Serum

Clinical Information: See Individual Unit Codes

Useful For: See Individual Unit Codes

Interpretation: See Individual Unit Codes

Reference Values:

INHIBIN A, TUMOR MARKER
Males: <2.0 pg/mL
Females
<11 years: <4.7 pg/mL
11-17 years: <97.5 pg/mL
Premenopausal: <97.5 pg/mL
Postmenopausal: <2.1 pg/mL

INHIBIN B
Males
0-23 months: <430 pg/mL
2-4 years: <269 pg/mL
5-7 years: <184 pg/mL
8-10 years: <214 pg/mL
11-13 years: <276 pg/mL
14-17 years: <273 pg/mL
Adults: <399 pg/mL

Females
0-23 months: <111 pg/mL
2-4 years: <44 pg/mL
5-7 years: <27 pg/mL
8-10 years: <67 pg/mL
11-13 years: <120 pg/mL
14-17 years: <136 pg/mL

Premenopausal
Follicular: <139 pg/mL
Luteal: <92 pg/mL
Postmenopausal: <10 pg/mL

Clinical References: See Individual Unit Codes

Inhibin A, Tumor Marker, Serum

Clinical Information: Inhibins are heterodimeric protein hormones secreted by granulosa cells of the ovary in the female and Sertoli cells of the testis in the male. They selectively suppress the secretion of pituitary follicle stimulating hormone (FSH) and also have local paracrine actions in the gonads. The inhibins consist of a dimer of 2 homologous subunits, an alpha subunit and either a beta A or beta B subunit, to form inhibin A and inhibin B, respectively. In females, inhibin A is primarily produced by the dominant follicle and corpus luteum; whereas inhibin B is predominantly produced by small developing follicles. Serum inhibin A and B levels fluctuate during the menstrual cycle. At menopause, with the depletion of ovarian follicles, serum inhibin A and B decrease to very low or undetectable levels. Ovarian cancer is classified into 3 types: epithelial, stromal sex cord, and germ cell tumors. Epithelial ovarian tumors account for 90% of cases and are further subdivided into: serous (70%), mucinous (10%-15%), and endometrioid (10%-15%) types. Granulosa cell tumors represent the majority of the stromal sex cord tumors, which account for 2% to 5% of all ovarian tumors. Elevations of serum inhibin A and B are detected in some patients with granulosa cell tumors. Inhibin A elevations have been reported in approximately 70% of granulosa cell tumors. In these patients, inhibin A levels tend to show a 6-fold to 7-fold increase over the reference range value. The frequency of elevated levels varies amongst studies, likely due to the different specificities of the antibodies used in the immunoassays. Inhibin A also appears to be suitable markers for epithelial tumors of the mucinous type with about 20% of cases having elevated inhibin A levels. In contrast, inhibin is not a very good marker in nonmucinous epithelial tumors. At best, total inhibin is elevated in 15% to 35% of nonmucinous epithelial ovarian cancer cases. Inhibin seems to be a complementary to cancer antigen 125 (CA 125) as an ovarian cancer marker. CA 125 is not as good of a tumor marker for mucinous and granulosa ovarian cell tumors. Inhibin shows a better performance in those 2 types of ovarian cancer. The majority of the studies for inhibin A and B as an ovarian cancer marker have been limited to postmenopausal women where the levels for both proteins are normally very low. Inhibin A has limited utility as an ovarian cancer marker in premenopausal women, where circulating levels are higher and fluctuate throughout the menstrual cycle and, therefore, are difficult to interpret.

Useful For: Aiding in the diagnosis of patients with granulosa cell tumors of the ovary when used in combination with inhibin B Monitoring of patients with granulosa cell tumors and epithelial mucinous-type tumors of the ovary known to secrete inhibin A

Interpretation: Inhibin A levels are elevated in approximately 70% of patients with granulosa cell tumors and in approximately 20% of patients with epithelial ovarian tumors. A normal inhibin A level does not rule out a mucinous or granulosa ovarian cell tumor. Testing for inhibin B in these cases might...
be informative as a higher proportion of mucinous or granulosa ovarian cell tumors will have an elevated inhibin B level. Consider ordering INHAB / Inhibin A and B, Tumor Marker, Serum. For monitoring of patients with known ovarian cancer, inhibin A levels decrease shortly after surgery. Elevations of inhibin A after treatment are suggestive of residual, recurrent, or progressive disease. In patients with recurrent disease, inhibin A elevation seems to be present earlier than clinical symptoms. Patients in remission show normal levels of inhibin A.

**Reference Values:**

<table>
<thead>
<tr>
<th>Group</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>&lt;2.0 pg/mL</td>
</tr>
<tr>
<td>Females</td>
<td></td>
</tr>
<tr>
<td>&lt;11 years</td>
<td>&lt;4.7 pg/mL</td>
</tr>
<tr>
<td>11-17 years</td>
<td>&lt;97.5 pg/mL</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>&lt;97.5 pg/mL</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>&lt;2.1 pg/mL</td>
</tr>
</tbody>
</table>


**INHB**

**Inhibin B, Serum**

**Clinical Information:** Inhibins are heterodimeric protein hormones secreted by granulosa cells of the ovary in females and Sertoli cells of the testis in males. Inhibins selectively suppress the secretion of pituitary follicle-stimulating hormone (FSH) and also have local paracrine actions in the gonads. The inhibins consist of a dimer of 2 homologous subunits, an alpha subunit and either a beta A or beta B subunit, to form inhibin A and inhibin B, respectively. In females, inhibin A is primarily produced by the dominant follicle and corpus luteum, whereas inhibin B is primarily produced by small developing follicles. Serum inhibin A and B levels fluctuate during the menstrual cycle. Inhibin A is low in the early follicular phase and rises at ovulation to maximum levels in the midluteal phase. In contrast, inhibin B levels increase early in the follicular phase to reach a peak coincident with the onset of the midfollicular phase decline in FSH levels. Inhibin B levels decrease in the late follicular phase. There is a short-lived peak of the hormone 2 days after the midcycle luteinizing hormone (LH) peak. Inhibin B levels remain low during the luteal phase of the cycle. The timing of the inhibin B rise suggests that it plays a role in regulation of folliculogenesis via a negative feedback on the production of FSH. At menopause, with the depletion of ovarian follicles, serum inhibin A and B decrease to very low or undetectable levels. Ovarian cancer is classified into 3 types: epithelial (80%), germ cell tumors (10%-15%), and stromal sex-cord tumors (5%-10%). Epithelial ovarian tumors are further subdivided into serous (70%), mucinous (10%-15%), and endometrioid (10%-15%) types. Granulosa cell tumors represent the majority of the stromal sex-cord tumors. Elevations of serum inhibin A and/or B are detected in some patients with granulosa cell tumors. Inhibin B elevations have been reported in 89% to 100% of patients with granulosa cell tumors. In those patients, inhibin B levels tend to be elevated about 60-fold over the reference range value. The frequency of elevated levels varies amongst studies, likely due to the different specificities of the antibodies used in the immunoassays. Inhibin B also appears to be a suitable serum marker for epithelial tumors of the mucinous type with about 55% to 60% having elevated inhibin B levels. In contrast, inhibin is not a very good marker in nonmucinous epithelial tumors. At best, total inhibin is elevated in 15% to 35% of nonmucinous epithelial ovarian cancer cases. Inhibin seems to be complementary to cancer antigen 125 (CA 125) as an ovarian cancer marker. CA 125 is not as good of a tumor marker for mucinous and granulosa ovarian cell tumors. Inhibin shows a better performance in those 2 types of ovarian cancer. The majority of the studies for inhibin A and B as an ovarian cancer marker have been limited to postmenopausal women where the levels of inhibin are normally very low. Inhibin levels vary in relation to the menstrual cycle and, therefore, are difficult to interpret in premenopausal women. Inhibin B has also been used as a marker of ovarian reserve. Every female is born with a specific number of follicles containing oocytes, a number that steadily and naturally declines with age. The number of follicles remaining in the ovary at any time is called the ovarian reserve. As ovarian reserve diminishes, it is increasingly more difficult for the hormones used...
for in vitro fertilization (IVF) to stimulate follicle development and, thus, the likelihood of successful oocyte retrieval, fertilization, and embryo transfer decreases, all leading to a lower chance of conceiving. As part of an infertility evaluation, attempts are made to estimate a woman's ovarian reserve. Tests to assess ovarian reserve include: day 3 FSH, day 3 inhibin B, and antimullerian hormone levels. The amount of inhibin B measured in serum during the early follicular phase of the menstrual cycle (day 3) directly reflects the number of follicles in the ovary. Therefore, the higher the inhibin B, the more ovarian follicles present. The level of inhibin B that predicts a poor response to IVF treatment has not been established with this assay. In males, inhibin B levels are higher in men with apparently normal fertility than in those with infertility and abnormal spermatogenesis. Serum inhibin B, when used in combination with FSH, is a more sensitive marker of spermatogenesis than FSH alone. However, the optimal level of inhibin B to assess male infertility has not been established.

Useful For: As an aid in the diagnosis of granulosa cell tumors and mucinous epithelial ovarian tumors Monitoring of patients with granulosa cell tumors and epithelial mucinous-type tumors of the ovary known to overexpress inhibin B As an adjunct to follicle-stimulating hormone testing during infertility evaluation

Interpretation: Inhibin B levels are elevated in approximately 89% to 100% of patients with granulosa cell tumors and in approximately 55% to 60% of patients with epithelial ovarian tumors. A normal inhibin B level does not rule out a mucinous or granulosa ovarian cell tumor. Testing for inhibin A in these cases might be informative. Consider ordering INHAB / Inhibin A and B, Tumor Marker, Serum. For monitoring of patients with known ovarian cancer, inhibin B levels decrease to very low or undetectable levels shortly after surgery. Elevations of inhibin B after treatment are suggestive of residual, recurrent, or progressive disease. In patients with recurrent disease, inhibin B elevation seems to be present earlier than clinical symptoms. Patients in remission show normal levels of inhibin B. For infertility evaluation, an inhibin B level in the postmenopausal range is suggestive of a diminished or depleted ovarian reserve.

Reference Values:
Males
0-23 months: <430 pg/mL
2-4 years: <269 pg/mL
5-7 years: <184 pg/mL
8-10 years: <214 pg/mL
11-13 years: <276 pg/mL
14-17 years: <273 pg/mL
Adults: <399 pg/mL
Females
0-23 months: <111 pg/mL
2-4 years: <44 pg/mL
5-7 years: <27 pg/mL
8-10 years: <67 pg/mL
11-13 years: <120 pg/mL
14-17 years: <136 pg/mL
Premenopausal
Follicular: <139 pg/mL
Luteal: <92 pg/mL
Postmenopausal: <10 pg/mL

**Insulin (Human), IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Insulin Antibodies, Serum

Clinical Information: The onset of autoimmune diabetes mellitus (type 1 diabetes mellitus) is preceded (and accompanied) by the appearance of autoantibodies to a variety of pancreatic islet cell antigens in serum, including insulin. The level of these autoantibodies is generally low and may even fall during follow-up. In genetically predisposed, but disease-free, individuals (first degree relatives of patients with type 1 diabetes or individuals with permissive HLA alleles), detection of multiple islet cell autoantibodies is a strong predictor for subsequent development of type 1 diabetes. Once type 1 diabetes has become fully manifest, insulin autoantibody levels usually fall to low or undetectable levels. However, after insulin therapy is initiated, autoantibody production may recur as a memory response. Insulin autoantibody production is more common when therapeutic insulin of animal origin is used (rarely used in contemporary practice). Larger therapeutic doses may be required because of antibody-induced insulin resistance. Insulin antibodies may be found in nondiabetic individuals complaining of hypoglycemic attacks. In this setting their presence can be an indicator of "factitious hypoglycemia" due to the surreptitious injection of insulin, rather than to a clinical problem (eg, insulinoma). However, insulin autoantibodies in nondiabetic subjects can occasionally develop without exposure to exogenous insulin and may rarely become a cause of episodic hypoglycemia. Anti-idiotypic autoantibodies against insulin autoantibodies have been demonstrated in some cases. Interaction of these antibodies with insulin autoantibodies could displace bound insulin from the insulin autoantibodies, resulting in hypoglycemia. In addition to IgG and IgM insulin autoantibodies, IgE antibodies (identified by the fluorescence enzyme immunoassay) may occur. IgE insulin autoantibodies result in immediate hypersensitivity reactions, such as urticaria, but do not lead to insulin resistance or hypoglycemia as can be seen with the IgG antibodies. This test only determines the presence of IgG and IgM antibodies, not IgE antibodies. In conjunction with family history, HLA-typing and measurement of other islet cell autoantibodies (glutamic acid decarboxylase [GAD65] antibody and islet cell antigen 2 antibody [IA-2]), insulin autoantibody testing helps predict the future development of type 1 diabetes in asymptomatic children, adolescents, and young adults. Inclusion of a recently described fourth autoantibody (zinc transporter 8, ZnT8) further enhances the prediction of type 1 diabetes occurrence and its distinction from type 2 diabetes.

Useful For: Predicting the future development of type 1 diabetes in asymptomatic children, adolescents, and young adults, when used in conjunction with family history, HLA-typing, and other autoantibodies, including GD65S/81596 Glutamic Acid Decarboxylase (GAD65) Antibody Assay, Serum and islet cell antigen 2 (IA-2) antibodies Differential diagnosis of type 1 versus type 2 diabetes Evaluating diabetics with insulin resistance in patients with established diabetes (type 1 or type 2) Investigation of hypoglycemia in nondiabetic subjects

Interpretation: Seropositivity (> or =0.03 nmol/L) in a patient never treated with insulin is consistent with predisposition to type 1 diabetes. Seropositivity is not as informative of type 2 diabetes status as other islet cell antibodies in patients who are receiving (or have received) insulin therapy because this antibody can arise secondary to therapy. It is thought that high levels of insulin autoantibodies might contribute to insulin resistance. A family history of type 1 diabetes, other organ-specific autoimmunity and a diabetes-permissive HLA phenotype strengthens the prediction of type 1 diabetes development. The detection of multiple islet cell antibodies is indicative of the likely development of future type 1 diabetes. In patients presenting with hypoglycemia, the presence of insulin autoantibodies may indicate surreptitious insulin administration or, rarely, insulin autoantibody-related hypoglycemia. The differential diagnosis cannot be made on the basis of insulin autoantibody detection alone. C-peptide and insulin measurements are always required in addition to insulin autoantibody measurements in the diagnosis of hypoglycemia.
**INSUL 70478**

**Insulin Immunostain, Technical Component Only**

**Clinical Information:** Insulin is a polypeptide hormone secreted by the beta cells of the islets of Langerhans in the pancreas. It promotes glycogen storage, formation of triglycerides, and synthesis of protein and nucleic acids. Cytoplasmic staining is seen in normal pancreatic islet beta cells and insulin secreting islet cell tumors.

**Useful For:** Aids in the identification of normal pancreatic islet beta cells and insulin secreting islet cell tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**INSFT 62990**

**Insulin, Free and Total, Serum**

**Clinical Information:** Insulin is produced by the beta cells of the pancreas. It regulates the uptake and utilization of glucose and is also involved in protein synthesis and triglyceride storage. Circulating insulin antibodies develop after diabetic patients are treated with exogenous insulin preparations. The presence of insulin antibodies has 2 main consequences: 1. Insulin antibodies will directly bind to insulin, making it unavailable for metabolic activity. 2. Insulin antibodies may adversely affect the binding characteristics of insulin in immunoassays, making reliable quantitation difficult. Free (bioactive) insulin could be measured after polyethylene glycol (PEG) precipitation of insulin antibodies and their bound insulin. If insulin antibodies are not present, the free and total insulin should be equivalent. The laboratory will report results of the total insulin (without PEG precipitation) and the free insulin (with PEG precipitation).

**Useful For:** Assessing free (bioactive) insulin concentrations in patients with known or suspected insulin antibodies

**Interpretation:** If insulin antibodies are not present, the free and total insulin should be equivalent. A significant difference between total and free insulin is suggestive of the presence of insulin antibodies. During prolonged fasting, when the patient's glucose is reduced to less than 40.0 mg/dL,
elevated insulin level plus elevated levels of proinsulin and C-peptide suggest insulinoma. In patients with insulin-dependent diabetes mellitus, insulin levels generally decline. In the early stage of noninsulin-dependent diabetes mellitus (NIDDM), insulin levels are either normal or elevated. In the late stage of NIDDM, insulin levels may also decline as levels of proinsulin decrease.

**Reference Values:**

- **Insulin, Free, S**
  2.6-24.9 mcIU/mL

- **Insulin, Total, S**
  2.6-24.9 mcIU/mL

**Clinical References:**


**Insulin, Serum**

**Clinical Information:** Insulin is a hormone produced by the beta cells of the pancreas. It regulates the uptake and utilization of glucose and is also involved in protein synthesis and triglyceride storage. Type 1 diabetes (insulin-dependent diabetes) is caused by insulin deficiency due to destruction of insulin-producing pancreatic islet (beta) cells. Type 2 diabetes (noninsulin dependent diabetes) is characterized by resistance to the action of insulin (insulin resistance). Insulin levels may be increased in patients with pancreatic beta cell tumors (insulinoma).

**Useful For:** Diagnosing insulinoma, when used in conjunction with proinsulin and C-peptide measurements Management of diabetes mellitus

**Interpretation:** During prolonged fasting, when the patient's glucose level is reduced to <40 mg/dL, elevated insulin level plus elevated levels of proinsulin and C-peptide suggest insulinoma. Insulin levels generally decline in patients with type 1 diabetes mellitus. In the early stage of type 2 diabetes, insulin levels are either normal or elevated. In the late stage of type 2 diabetes, insulin levels decline. In normal individuals, insulin levels parallel blood glucose levels. To compare insulin and C-peptide concentrations (ie, insulin to C-peptide ratio): -Convert insulin to pmol/L: insulin concentration in mcIU/mL x 6.945 = insulin concentration in pmol/L. -Convert C-peptide to pmol/L: C-peptide concentration in ng/mL x 331 = C-peptide concentration in pmol/L.

**Reference Values:**

2.6-24.9 mcIU/mL

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.


**Insulin-Like Growth Factor 1 (IGF1), LC-MS and Insulin-Like Growth Factor-Binding Protein 3 (IGFBP3) Growth Panel**

**Clinical Information:** Insulin-like growth factor 1 (IGF1) is a 70-amino acid polypeptide (molecular weight 7.6 kDa). IGF1 is a member of a family of closely related growth factors with high homology to insulin that signal through a corresponding group of highly homologous tyrosine kinase receptors. IGF1 is produced by many tissues, but the liver is the main source of circulating IGF1. IGF1 is the major mediator of the anabolic and growth-promoting effects of growth hormone (GH). IGF1 is transported by IGF-binding proteins, in particular insulin-like growth factor-binding protein 3 (IGFBP3), which also...
controls its bioavailability and half-life. IGFBP3 is a 264-amino acid peptide (MW 29kD) produced by the liver. It is the most abundant of a group of IGFBPs that transport, and control bioavailability and half-life of IGFs, in particular IGF1, the major mediator of the anabolic- and growth-promoting effects of GH. In addition to its IGF binding-function, IGFBP3 also exhibits intrinsic growth-regulating effects that are not yet fully understood, but have evoked interest with regards to a possible role of IGFBP3 as a prognostic tumor marker. Noncomplexed IGF1 and IGFBP3 have short half-lives (t1/2) of 10 and 30 to 90 minutes, respectively, while the IGFBP3/IGF1 complex is cleared with a much slower t1/2 of 12 hours. The secretion patterns of IGF1 and IGFBP3 mimic each other, their respective syntheses being controlled by GH. Unlike GH secretion, which is pulsatile and demonstrates significant diurnal variation, IGF1 and IGFBP3 levels show only minor fluctuations. IGF1 and IGFBP3 serum levels, therefore, represent a stable and integrated measurement of GH production and tissue effect. Low IGF1 and IGFBP3 levels are observed in GH deficiency or GH resistance. If acquired in childhood, these conditions result in short stature. Childhood GH deficiency can be an isolated abnormality or associated with deficiencies of other pituitary hormones. Some of the latter cases may be due to pituitary or hypothalamic tumors, or result from cranial radiation or intrathecal chemotherapy for childhood malignancies. Most GH resistance in childhood is mild to moderate, with causes ranging from poor nutrition to severe systemic illness (eg, renal failure). These individuals may have IGF1 and IGFBP3 levels within the reference range. Severe childhood GH resistance is rare and usually due to defects of the GH-receptor, its downstream signaling cascades, or deleterious mutations in IGF1, its binding proteins, or its receptor signaling cascades. Both GH deficiency and mild-to-moderate GH resistance can be treated with recombinant human GH (rhGH) injections, while severe resistance will usually not respond to GH. However, such patients might respond to recombinant IGF1 therapy, unless the underlying defect is in the IGF1 receptor or its downstream signaling systems. The exact prevalence and causes of adult GH resistance are uncertain, but adult GH deficiency is seen mainly in pituitary tumor patients. It is associated with decreased muscle bulk and increased cardiovascular morbidity and mortality, but replacement therapy remains controversial. Elevated serum IGF1 and IGFBP3 levels often indicate a sustained overproduction of GH, or excessive rhGH therapy. Endogenous GH excess is caused mostly by GH-secreting pituitary adenomas, resulting in gigantism, if acquired before epiphyseal closure, and in acromegaly thereafter. Both conditions are associated with generalized organomegaly, hypertension, diabetes, cardiomyopathy, osteoarthritis, compression neuropathies, a mild increase in cancer risk (breast, colon, prostate, lung), and diminished longevity. It is plausible, but unproven, that long-term rhGH overtreatment may result in similar adverse outcomes. Malnutrition results in low serum IGF1 concentrations, which recover with restoration of adequate nutrition.

**Useful For:** Diagnosing growth disorders Diagnosing adult growth hormone deficiency Monitoring of recombinant human growth hormone treatment Insulin-like growth factor binding protein 3 can be used as a possible adjunct to insulin-like growth factor 1 and growth hormone in the diagnosis and follow-up of acromegaly and gigantism.

**Interpretation:** Both insulin-like growth factor 1 (IGF1) and insulin-like growth factor binding protein 3 (IGFBP3) measurements can be used to assess growth hormone (GH) excess or deficiency. However, for all applications, IGF1 measurement has generally been shown to have superior diagnostic sensitivity and specificity, and should be used as the primary test. In particular, in the diagnosis and follow-up of acromegaly and gigantism, IGFBP3 measurement adds little if anything to IGF1 testing. The combination of IGF1 and IGFBP3 measurements might offer some benefits over either analyte alone in the diagnosis of GH deficiency and resistance, and in the monitoring of recombinant human GH (rhGH) therapy. Serum IGF1 and IGFBP3 concentrations below the 2.5th percentile (Standard deviation score, Z-score of < -2) for age are consistent with GH deficiency or severe GH resistance, but patients with incomplete GH deficiency or mild-to-moderate GH resistance may have levels within the reference range. In GH deficiency, GH levels may also be low and can show suboptimal responses in stimulation tests (eg exercise, clonidine, arginine, ghrelin, growth hormone-releasing hormone, insulin-induced hypoglycemia), while in severe GH resistance, GH levels might be substantially elevated. However, dynamic GH testing is not always necessary for diagnosis. If it is undertaken, it should be performed and interpreted in endocrine testing centers under the supervision of a pediatric or adult endocrinologist. The aim of both pediatric and adult GH replacement therapy is to achieve IGF1 and IGFBP3 levels within the reference range, ideally within the middle-to-upper third. Higher levels are rarely associated with any further therapeutic gains, but could potentially lead to long-term problems of GH excess. Elevated IGF1 and IGFBP3 levels support the diagnosis of acromegaly or gigantism in
individuals with appropriate symptoms or signs. In successfully treated patients, both levels should be within the normal range, ideally within the lower third. In both diagnosis and follow-up, IGF1 levels correlate better with clinical disease activity than IGFBP3 levels. After transphenoidal removal of pituitary tumors in patients with acromegaly, IGF-I concentration starts to decrease and returns to normal levels in most patients postoperatively by the fourth day. Persons with anorexia or malnutrition have low values of IGF1. IGF1 is a more sensitive indicator than prealbumin, retinol-binding protein, or transferrin for monitoring nutritional repletion.

**Reference Values:**
**INSULIN-LIKE GROWTH FACTOR 1**

**Males:**
- 0-11 months: 18-156 ng/mL
- 1 year: 14-203 ng/mL
- 2 years: 16-222 ng/mL
- 3 years: 22-229 ng/mL
- 4 years: 30-236 ng/mL
- 5 years: 39-250 ng/mL
- 6 years: 47-275 ng/mL
- 7 years: 54-312 ng/mL
- 8 years: 61-356 ng/mL
- 9 years: 67-405 ng/mL
- 10 years: 73-456 ng/mL
- 11 years: 79-506 ng/mL
- 12 years: 84-551 ng/mL
- 13 years: 90-589 ng/mL
- 14 years: 95-618 ng/mL
- 15 years: 99-633 ng/mL
- 16 years: 104-633 ng/mL
- 17 years: 107-615 ng/mL
- 18-22 years: 91-442 ng/mL
- 23-25 years: 66-346 ng/mL
- 26-30 years: 60-329 ng/mL
- 31-35 years: 54-310 ng/mL
- 36-40 years: 48-292 ng/mL
- 41-45 years: 44-275 ng/mL
- 46-50 years: 40-259 ng/mL
- 51-55 years: 37-245 ng/mL
- 56-60 years: 34-232 ng/mL
- 61-65 years: 33-220 ng/mL
- 66-70 years: 32-209 ng/mL
- 71-75 years: 32-200 ng/mL
- 76-80 years: 33-192 ng/mL
- 81-85 years: 33-185 ng/mL
- 86-90 years: 33-179 ng/mL
- >91 years: 32-173 ng/mL

**Females:**
- 0-11 months: 14-192 ng/mL
- 1 year: 23-243 ng/mL
- 2 years: 28-256 ng/mL
- 3 years: 31-249 ng/mL
- 4 years: 33-237 ng/mL
- 5 years: 36-234 ng/mL
- 6 years: 39-246 ng/mL
- 7 years: 44-279 ng/mL
- 8 years: 51-334 ng/mL
- 9 years: 61-408 ng/mL
- 10 years: 73-495 ng/mL
11 years: 88-585 ng/mL
12 years: 104-665 ng/mL
13 years: 120-719 ng/mL
14 years: 136-729 ng/mL
15 years: 147-691 ng/mL
16 years: 153-611 ng/mL
17 years: 149-509 ng/mL
18-22 years: 85-370 ng/mL
23-25 years: 73-320 ng/mL
26-30 years: 66-303 ng/mL
31-35 years: 59-279 ng/mL
36-40 years: 54-258 ng/mL
41-45 years: 49-240 ng/mL
46-50 years: 44-227 ng/mL
51-55 years: 40-217 ng/mL
56-60 years: 37-208 ng/mL
61-65 years: 35-201 ng/mL
66-70 years: 34-194 ng/mL
71-75 years: 34-187 ng/mL
76-80 years: 34-182 ng/mL
81-85 years: 34-177 ng/mL
86-90 years: 33-175 ng/mL
> or =91 years: 25-179 ng/mL

Tanner Stage reference ranges:

Males
Stage I: 81-255 ng/mL
Stage II: 106-432 ng/mL
Stage III: 245-511 ng/mL
Stage IV: 223-578 ng/mL
Stage V: 227-518 ng/mL

Females
Stage I: 86-323 ng/mL
Stage II: 118-451 ng/mL
Stage III: 258-529 ng/mL
Stage IV: 224-586 ng/mL
Stage V: 188-512 ng/mL


Note: Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

INSULIN-LIKE GROWTH FACTOR-BINDING PROTEIN 3
1-7 days: < or =0.7 mcg/mL
8-14 days: 0.5-1.4 mcg/mL
15 days-11 months: unavailable
1 year: 0.7-3.6 mcg/mL
2 years: 0.8-3.9 mcg/mL
3 years: 0.9-4.3 mcg/mL
4 years: 1.0-4.7 mcg/mL
5 years: 1.1-5.2 mcg/mL
<table>
<thead>
<tr>
<th>Age Group</th>
<th>IGF-1 Range (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 years</td>
<td>1.3-5.6</td>
</tr>
<tr>
<td>7 years</td>
<td>1.4-6.1</td>
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<tr>
<td>8 years</td>
<td>1.6-6.5</td>
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<td>9 years</td>
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<td>13 years</td>
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<td>2.5-5.1</td>
</tr>
<tr>
<td>81-85 years</td>
<td>2.2-4.5</td>
</tr>
</tbody>
</table>

**Tanner Stages:**

**Males**
- Stage I: 1.4-5.2 mcg/mL
- Stage II: 2.3-6.3 mcg/mL
- Stage III: 3.1-8.9 mcg/mL
- Stage IV: 3.7-8.7 mcg/mL
- Stage V: 2.6-8.6 mcg/mL

**Females**
- Stage I: 1.2-6.4 mcg/mL
- Stage II: 2.8-6.9 mcg/mL
- Stage III: 3.9-9.4 mcg/mL
- Stage IV: 3.3-8.1 mcg/mL
- Stage V: 2.7-9.1 mcg/mL

Note: Puberty onset, ie, the transition from Tanner stage 1 (prepubertal) to Tanner stage 2 (early pubertal), occurs for girls at a median age of 10.5 (+/-2) years and for boys at a median age of 11.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African-American girls. By contrast, for boys there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage 5 (young adult) should be reached by age 18.

**Clinical References:**

**FIGF2**

**Insulin-like Growth Factor 2 (IGF-2)**

**Reference Values:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Range (ng/mL)</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepubertal</td>
<td>258 â€“ 882</td>
<td>570</td>
</tr>
<tr>
<td>Pubertal</td>
<td>273 â€“ 892</td>
<td>583</td>
</tr>
<tr>
<td>Adults</td>
<td>333 â€“ 967</td>
<td>650</td>
</tr>
</tbody>
</table>

**IGFMS**

**Insulin-Like Growth Factor-1, LC-MS, Serum**

**Clinical Information:** Insulin-like growth factor 1 (IGF1) is a 70-amino acid polypeptide (molecular weight kDa; Uniprot Accession P05019 [aa 49-118]). IGF1 is a member of a family of closely related growth factors with high homology to insulin that signal through a corresponding group of highly homologous tyrosine kinase receptors. IGF1 is produced by many tissues, but the liver is the main source of circulating IGF1. IGF1 is the major mediator of the anabolic and growth-promoting effects of growth hormone (GH). IGF1 is transported by IGF-binding proteins, in particular insulin-like growth factor-binding protein 3 (IGFBP3), which also controls its bioavailability and half-life. Noncomplexed IGF1 and IGFBP3 have short half-lives (t1/2) of 10 and 30 to 90 minutes, respectively, while the IGFBP3/IGF1 complex is cleared with a much slower t1/2 of 12 hours. The secretion patterns of IGF1 and IGFBP3 mimic each other, their respective syntheses being controlled by GH. Unlike GH secretion, which is pulsatile and demonstrates significant diurnal variation, IGF1 and IGFBP3 levels show only minor fluctuations. IGF1 and IGFBP3 serum levels, therefore, represent a stable and integrated measurement of GH production and tissue effect. Low IGF1 and IGFBP3 levels are observed in GH deficiency or GH resistance. If acquired in childhood, these conditions result in short stature. Childhood GH deficiency can be an isolated abnormality or associated with deficiencies of other pituitary hormones. Some of the latter cases may be due to pituitary or hypothalamic tumors, or result from cranial radiation or intrathecal chemotherapy for childhood malignancies. Most GH resistance in childhood is mild-to-moderate, with causes ranging from poor nutrition to severe systemic illness (e.g., renal failure). These individuals may have IGF1 and IGFBP3 levels within the reference range. Severe childhood GH resistance is rare and usually due to defects of the GH-receptor, its downstream signaling cascades, or deleterious mutations in IGF1, its binding proteins, or its receptor signaling cascades. Both GH deficiency and mild-to-moderate GH resistance can be treated with recombinant human GH (rhGH) injections, while severe resistance will usually not respond to GH. However, such patients might respond to recombinant IGF1 therapy, unless the underlying defect is in the IGF1 receptor or its downstream signaling systems. The exact prevalence and causes of adult GH resistance are uncertain, but adult GH deficiency is seen mainly in pituitary tumor patients. It is associated with decreased muscle bulk and increased cardiovascular morbidity and mortality, but replacement therapy remains controversial. Elevated serum IGF1 and IGFBP3 levels often indicate a sustained overproduction of GH, or excessive rhGH therapy. Endogenous GH excess is caused mostly by GH-secreting pituitary adenomas, resulting in gigantism, if acquired before epiphyseal closure, and in acromegaly thereafter. Both conditions are associated with generalized organomegaly, hypertension, diabetes, cardiomyopathy, osteoarthritis, compression neuropathies, a mild increase in cancer risk (breast, colon, prostate, lung), and diminished longevity. It is plausible, but unproven, that long-term rhGH overtreatment may result in similar adverse outcomes. Malnutrition results in low serum IGF1 concentrations, which recover with...
restoration of adequate nutrition.

**Useful For:** Evaluation of growth disorders Evaluation of growth hormone deficiency or excess in children and adults Monitoring of recombinant human growth hormone treatment Follow-up of individuals with acromegaly and gigantism

**Interpretation:** Both insulin-like growth factor 1 (IGF1) and insulin-like growth factor-binding protein 3 (IGFBP3) measurements can be used to assess growth hormone (GH) excess or deficiency. However, for all applications, IGF1 measurement has generally been shown to have superior diagnostic sensitivity and specificity, and should be used as the primary test. In particular, in the diagnosis and follow-up of acromegaly and gigantism, IGFBP3 measurement adds little if anything to IGF1 testing. The combination of IGF1 and IGFBP3 measurements might offer some benefits over either analyte alone in the diagnosis of GH deficiency and resistance, and in the monitoring of recombinant human GH (rhGH) therapy. Serum IGF1 and IGFBP3 concentrations below the 2.5th percentile (Standard deviation score, Z-score of <-2) for age are consistent with GH deficiency or severe GH resistance, but patients with incomplete GH deficiency or mild-to-moderate GH resistance may have levels within the reference range. In GH deficiency, GH levels may also be low and can show suboptimal responses in stimulation tests (e.g., exercise, clonidine, arginine, ghrelin, growth hormone-releasing hormone, insulin-induced hypoglycemia), while in severe GH resistance, GH levels might be substantially elevated. However, dynamic GH testing is not always necessary for diagnosis. If it is undertaken, it should be performed and interpreted in endocrine testing centers under the supervision of a pediatric or adult endocrinologist. The aim of both pediatric and adult GH replacement therapy is to achieve IGF1 and IGFBP3 levels within the reference range, ideally within the middle-to-upper third. Higher levels are rarely associated with any further therapeutic gains, but could potentially lead to long-term problems of GH excess. Elevated IGF1 and IGFBP3 levels support the diagnosis of acromegaly or gigantism in individuals with appropriate symptoms or signs. In successfully treated patients, both levels should be within the normal range, ideally within the lower third. In both diagnosis and follow-up, IGF1 levels correlate better with clinical disease activity than IGFBP3 levels. After transsphenoidal removal of pituitary tumors in patients with acromegaly, IGF-1 concentration starts to decrease and returns to normal levels in most patients postoperatively by the fourth day. Persons with anorexia or malnutrition have low values of IGF1. IGF1 is a more sensitive indicator than prealbumin, retinol-binding protein, or transferrin for monitoring nutritional repletion.

**Reference Values:**

**Males:**
- 0-11 months: 18-156 ng/mL
- 1 year: 14-203 ng/mL
- 2 years: 16-222 ng/mL
- 3 years: 22-229 ng/mL
- 4 years: 30-236 ng/mL
- 5 years: 39-250 ng/mL
- 6 years: 47-275 ng/mL
- 7 years: 54-312 ng/mL
- 8 years: 61-356 ng/mL
- 9 years: 67-405 ng/mL
- 10 years: 73-456 ng/mL
- 11 years: 79-506 ng/mL
- 12 years: 84-551 ng/mL
- 13 years: 90-589 ng/mL
- 14 years: 95-618 ng/mL
- 15 years: 99-633 ng/mL
- 16 years: 104-633 ng/mL
- 17 years: 107-615 ng/mL
- 18-22 years: 91-442 ng/mL
- 23-25 years: 66-346 ng/mL
- 26-30 years: 60-329 ng/mL
- 31-35 years: 54-310 ng/mL
- 36-40 years: 48-292 ng/mL
- 41-45 years: 44-275 ng/mL

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46-50 years: 40-259 ng/mL
51-55 years: 37-245 ng/mL
56-60 years: 34-232 ng/mL
61-65 years: 33-220 ng/mL
66-70 years: 32-209 ng/mL
71-75 years: 32-200 ng/mL
76-80 years: 33-192 ng/mL
81-85 years: 33-185 ng/mL
86-90 years: 33-179 ng/mL
>91 years: 32-173 ng/mL

Females:
0-11 months: 14-192 ng/mL
1 year: 23-243 ng/mL
2 years: 28-256 ng/mL
3 years: 31-249 ng/mL
4 years: 33-237 ng/mL
5 years: 36-234 ng/mL
6 years: 39-246 ng/mL
7 years: 44-279 ng/mL
8 years: 51-334 ng/mL
9 years: 61-408 ng/mL
10 years: 73-495 ng/mL
11 years: 88-585 ng/mL
12 years: 104-665 ng/mL
13 years: 120-719 ng/mL
14 years: 136-729 ng/mL
15 years: 147-691 ng/mL
16 years: 153-611 ng/mL
17 years: 149-509 ng/mL
18-22 years: 85-370 ng/mL
23-25 years: 73-320 ng/mL
26-30 years: 66-303 ng/mL
31-35 years: 59-279 ng/mL
36-40 years: 54-258 ng/mL
41-45 years: 49-240 ng/mL
46-50 years: 44-227 ng/mL
51-55 years: 40-217 ng/mL
56-60 years: 37-208 ng/mL
61-65 years: 35-201 ng/mL
66-70 years: 34-194 ng/mL
71-75 years: 34-187 ng/mL
76-80 years: 34-182 ng/mL
81-85 years: 34-177 ng/mL
86-90 years: 33-175 ng/mL
> or =91 years: 32-173 ng/mL

Tanner Stage reference ranges:

Males
Stage I: 81-255 ng/mL
Stage II: 106-432 ng/mL
Stage III: 245-511 ng/mL
Stage IV: 223-578 ng/mL
Stage V: 227-518 ng/mL

Females
Stage I: 86-323 ng/mL
Stage II: 118-451 ng/mL
Stage III: 258-529 ng/mL
Stage IV: 224-586 ng/mL
Stage V: 188-512 ng/mL


Note: Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.


Insulin-Like Growth Factor-Binding Protein 3 (IGFBP-3), Serum

Clinical Information: Insulin-like growth factor-binding protein-3 (IGFBP-3) is a 264-amino acid peptide (MW 29 kD) produced by the liver. It is the most abundant of a group of IGFBPs that transport, and control bioavailability and half-life of insulin-like growth factors (IGF), in particular IGF-1, the major mediator of the anabolic- and growth-promoting effects of growth hormone (GH). Noncomplexed IGFBP-3 and IGF-1 have short half-lives (t1/2) of 30 to 90 minutes, and 10 minutes, respectively, while the IGFBP-3/IGF-1 complex is cleared with a much slower t1/2 of 12 hours. In addition to its IGF-binding function, IGFBP-3 also exhibits intrinsic growth-regulating effects that are not yet fully understood, but have evoked interest with regards to a possible role of IGFBP-3 as a prognostic tumor marker. The secretion patterns of IGFBP-3 and IGF-1 mimic each other; their respective syntheses are primarily controlled by GH. Unlike GH secretion, which is pulsatile and demonstrates significant diurnal variation, IGFBP-3 and IGF-1 levels show only minor fluctuations. IGFBP-3 and IGF-1 serum levels therefore represent a stable and integrated measurement of GH production and tissue effect. Low IGFBP-3 and IGF-1 levels are observed in GH deficiency or GH resistance. If acquired in childhood, these conditions result in short stature. Childhood GH deficiency can be an isolated abnormality or associated with deficiencies of other pituitary hormones. Some of the latter cases may be due to pituitary or hypothalamic tumors, or result from cranial radiation or intrathecal chemotherapy for childhood malignancies. Most GH resistance in childhood is mild to moderate, with causes ranging from poor nutrition to severe systemic illness (eg, renal failure). These individuals may have IGF-1 and IGFBP-3 levels within the reference range. Severe childhood GH resistance is rare and usually due to GH-receptor defects. Both GH deficiency and mild-to-moderate GH resistance can be treated with recombinant human GH (rhGH) injections. The prevalence and causes of adult GH resistance are uncertain, but adult GH deficiency is seen mainly in pituitary tumor patients. It is associated with decreased muscle bulk and increased cardiovascular morbidity and mortality, but replacement therapy remains controversial. Elevated serum IGFBP-3 and IGF-1 levels indicate a sustained overproduction of GH, or excessive rhGH therapy. Endogenous GH excess is caused mostly by GH-secreting pituitary adenomas, resulting in gigantism, if acquired before epiphyseal closure, and in acromegaly thereafter. Both conditions are associated with generalized organomegaly, hypertension, diabetes, cardiomyopathy, osteoarthritis, compression neuropathies, a mild increase in cancer risk, and diminished longevity. It is plausible, but
unproven, that long-term rhGH-overtreatment may result in similar adverse outcomes.

**Useful For:** Diagnosing growth disorders Diagnosing adult growth hormone deficiency Monitoring of recombinant human growth hormone treatment As a possible adjunct to insulin-like growth factor 1 and growth hormone in the diagnosis and follow-up of acromegaly and gigantism

**Interpretation:** For all applications, insulin-like growth factor 1 (IGF-1) measurement has generally been shown to have superior diagnostic sensitivity and specificity compared with insulin-like growth factor-binding protein 3 (IGFBP-3). IGFBP-3 testing should, therefore, usually be combined with IGF-1 testing. The combination of IGF-1 and IGFBP-3 measurements appears superior to determining either analyte alone in the diagnosis of growth hormone (GH) deficiency and resistance, and in the monitoring of recombinant human GH therapy. By contrast, in the diagnosis and follow-up of acromegaly and gigantism, IGFBP-3 measurement adds little if anything to IGF-1 testing. IGF-1 and IGFBP-3 levels below the 2.5th percentile for age are consistent with GH deficiency or severe resistance, but patients with incomplete GH deficiency or mild-to-moderate GH resistance may have levels within the reference range. In GH deficiency, GH levels are also low and show suboptimal responses in stimulation tests (eg, exercise, clonidine, arginine, ghrelin, growth hormone-releasing hormone, insulin-induced hypoglycemia), while in severe GH resistance, GH levels are substantially elevated. However, dynamic GH testing is not always necessary for diagnosis. If it is undertaken, it should be performed and interpreted in endocrine testing centers under the supervision of an endocrinologist. The aim of both pediatric and adult GH replacement therapy is to achieve IGF-1 and IGFBP-3 levels within the reference range, ideally within the middle to upper third. Higher levels are rarely associated with any further therapeutic gains, but could potentially lead to long-term problems of GH excess. Elevated IGF-1 and IGFBP-3 levels support the diagnosis of acromegaly or gigantism in individuals with appropriate symptoms or signs. In successfully treated patients, both levels should be within the normal range, ideally within the lower third. In both diagnosis and follow-up, IGF-1 levels correlate better with clinical disease activity than IGFBP-3 levels.

**Reference Values:**

- 1-7 days: < or =0.7 mcg/mL
- 8-14 days: 0.5-1.4 mcg/mL
- 15 days-11 months: unavailable
- 1 year: 0.7-3.6 mcg/mL
- 2 years: 0.8-3.9 mcg/mL
- 3 years: 0.9-4.3 mcg/mL
- 4 years: 1.0-4.7 mcg/mL
- 5 years: 1.1-5.2 mcg/mL
- 6 years: 1.3-5.6 mcg/mL
- 7 years: 1.4-6.1 mcg/mL
- 8 years: 1.6-6.5 mcg/mL
- 9 years: 1.8-7.1 mcg/mL
- 10 years: 2.1-7.7 mcg/mL
- 11 years: 2.4-8.4 mcg/mL
- 12 years: 2.7-8.9 mcg/mL
- 13 years: 3.1-9.5 mcg/mL
- 14 years: 3.3-10 mcg/mL
- 15 years: 3.5-10 mcg/mL
- 16 years: 3.4-9.5 mcg/mL
- 17 years: 3.2-8.7 mcg/mL
- 18 years: 3.1-7.9 mcg/mL
- 19 years: 2.9-7.3 mcg/mL
- 20 years: 2.9-7.2 mcg/mL
- 21-25 years: 3.4-7.8 mcg/mL
- 26-30 years: 3.5-7.6 mcg/mL
- 31-35 years: 3.5-7 mcg/mL
- 36-40 years: 3.4-6.7 mcg/mL
- 41-45 years: 3.3-6.6 mcg/mL
- 46-50 years: 3.3-6.7 mcg/mL
- 51-55 years: 3.4-6.8 mcg/mL

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
56-60 years: 3.4-6.9 mcg/mL
61-65 years: 3.2-6.6 mcg/mL
66-70 years: 3.0-6.2 mcg/mL
71-75 years: 2.8-5.7 mcg/mL
76-80 years: 2.5-5.1 mcg/mL
81-85 years: 2.2-4.5 mcg/mL

Tanner Stages:

Males
Stage I: 1.4-5.2 mcg/mL
Stage II: 2.3-6.3 mcg/mL
Stage III: 3.1-8.9 mcg/mL
Stage IV: 3.7-8.7 mcg/mL
Stage V: 2.6-8.6 mcg/mL

Females
Stage I: 1.2-6.4 mcg/mL
Stage II: 2.3-6.9 mcg/mL
Stage III: 3.6-9.0 mcg/mL
Stage IV: 3.3-8.1 mcg/mL
Stage V: 2.3-9.1 mcg/mL

Note: Puberty onset, ie, the transition from Tanner stage I (prepubertal) to Tanner stage II (early pubertal), occurs for girls at a median age of 10.5 (+/-2) years and for boys at a median age of 11.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African-American girls. By contrast, for boys there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

Clinical References:

**INSM1**

**Insulinoma-Associated Protein 1 (INSM1), Immunostain, Technical Component Only**

**Clinical Information:** Insulinoma-associated protein 1 (INSM1) is a transcription factor that plays a role in neurogenesis and neuroendocrine (NE) cell differentiation. INS1 expression is useful in the diagnosis of NE tumors and has been shown to be more sensitive and specific compared to other NE markers.

**Useful For:** Aiding in the identification of neuroendocrine tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist is required order PATHC / Pathology Consultation. The positive and negative controls are verified as showing appropriate immunoreactivity. If
a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**INI1 70477**

### Integrase Interactor 1 (INI1/BAF47) Immunostain, Technical Component Only

**Clinical Information:** Chromatin remodeling complexes play an important role in regulation of transcription by modulating access of proteins to DNA. Loss of function of these complexes has been implicated in human cancers. Integrase interactor 1 (INI1) is a member of the SWI/SNF chromatin remodeling complex. Studies have demonstrated point mutations and deletions of the INI1/BAF47 gene in pediatric rhabdoid tumors, rhabdomyosarcoma, chronic myeloid leukemia, as well as central nervous system tumors such as medulloblastomas and choroid plexus carcinomas. In these cases, loss of nuclear staining for INI1/BAF47 is seen. In normal tissues, nuclear expression of INI1/BAF47 should be present in all cell types.

**Useful For:** Part of a panel of immunostains where loss of staining can be used as a marker of various neoplasms

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**FIFNY 57586**

### Interferon-gamma (IFN-y) Serum

**Reference Values:** <2.0 pg/mL

**FINTA 91708**

### Interleukin 1a

**Clinical Information:** The Interleukins belong to the family termed cytokines. They are peptides
used by immune and inflammatory cells to communicate and control cell operations. The cytokines have some similar actions to the Growth Factors but Growth Factors regulate proliferation of non-immune cells. Interleukin 1a is a 17,500 molecular weight peptide derived primarily from macrophages, fibroblasts, endothelial cells, and B cells. The major target cells are T and B cells, Fibroblasts, and Hepatocytes. Interleukin 1a shares a receptor with Interleukin 1b although they are significantly different structurally. Interleukin 1a promotes antigen specific immune responses, inflammation, Prostaglandin secretion, Colony Stimulating Factors, proteoglycanase, collagenase, and gelatinase activity, and release of Interleukin 2 from T cells. Levels are stimulated by liposaccharide, endotoxins, inflammatory agents, lectin, Tumor Necrosis Factor, and Interferons. Levels are suppressed by Corticosteroids, Prostaglandin E2, and suppressant lymphocytes.

Reference Values:
Less than 3.9 pg/mL


FINTB
91719

Interleukin 1b

Clinical Information: The Interleukins belong to the family termed cytokines. They are peptides used by immune and inflammatory cells to communicate and control cell operations. The cytokines have some similar actions to the Growth Factors but Growth Factors regulate proliferation of non-immune cells. Interleukin 1b is a 17,500 molecular weight peptide derived primarily from macrophages, fibroblasts, endothelial cells, and B cells. The major target cells are T and B cells, Fibroblasts, and Hepatocytes and it has pyrogenic activity. Interleukin 1b shares a receptor with Interleukin 1a although they are significantly different structurally. Interleukin 1b promotes antigen specific immune responses, inflammation, secretion, Colony Stimulating Factors, proteoglycanase, collagenase, and gelatinase activity, acute phase response, and cartilage resorption. Interleukin 1b increases accumulation of cell-associated and extracellular arachidonic acid, and induces release of Interleukin 6.

Reference Values:
Less than 1.0 pg/mL


FIL2M
57826

Interleukin 2

Interpretation: Interpretive Information: Cytokines Results are to be used for research purposes or in attempts to understand the pathophysiology of immune, infectious, or inflammatory disorders.

Reference Values:
<=12 pg/mL

FIL2S
57825

Interleukin 2 Receptor (CD25), Soluble

Interpretation: Interpretive Information: Cytokines Results are used to understand the pathophysiology of immune, infectious, or inflammatory disorders or may be used for research purposes.

Reference Values:
IL28V 97395

Interleukin 28B (IL28B) Variant (rs12979860), Varies

Clinical Information: Individuals with hepatitis C virus (HCV) genotype 1 infections have variable responses to treatment with pegylated-interferon and ribavirin combination therapy. Some individuals will respond to treatment with sustained viral response, while other patients have poor response and fail to achieve sustained viral clearance. Response to pegylated-interferon and ribavirin combination therapy in HCV genotype 1-infected individuals has been found to be closely associated with a single-nucleotide polymorphism (SNP), designated rs12979860, located 3 kilobases upstream from the interleukin 28B gene locus (IL28B, also known as IFNL3) present on human chromosome 19. HCV genotype 1-infected individuals with the CC genotype, as compared to either the CT or TT genotypes, of this SNP in IL28B have approximately 2- to 3-fold greater rates of sustained viral response to combined pegylated-interferon and ribavirin therapy (1). Similar increases in sustained viral response rates were observed across various racial groups, including European Americans (95% CI, 1.8- to 2.3-fold), African Americans (95% CI, 1.9- to 4.7-fold), and Hispanics (95% CI, 1.4- to 3.2-fold).(1) The CC genotype has also been associated with a 3-fold increase in rate of spontaneous clearance of HCV.(2, 4) The SNP in IL28B is only one of many factors that can influence response rates to pegylated-interferon and ribavirin combination therapy in HCV genotype 1 infection, and the SNP genotype result should be interpreted in the context of other clinical factors present in a given patient. Frequency of the rs12979860 C allele varies across different racial and ethnic groups. The rs12979860 C variant is most frequently present in individuals from East Asia (allele frequency >0.9) and least common in individuals of African origin (allele frequency 0.2-0.5).(2) In a recent US-based study, the favorable CC genotype was observed in 37% of Caucasians, 29% Hispanics, and 14% of African Americans tested. The mechanism by which the IL28B genotype mediates response to pegylated-interferon and ribavirin combination therapy among HCV genotype 1-infected individuals is not yet understood and is the subject of intense ongoing research. The impact of the IL28B-related polymorphism on response rates in patients infected with HCV genotypes other than genotype 1 is still being investigated.

Useful For: Predicting responsiveness of genotype 1 hepatitis C viral infections to combined pegylated-interferon and ribavirin-based therapies in whole blood specimens

Interpretation: An interpretative report will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References:

IL5P 36519

Interleukin 5, Plasma

Clinical Information: Interleukin-5 (IL-5) is a homodimer composed of two 20-kD subunits.(1) It is expressed primarily by CD4+ Th2 (helper T cells, subset 2) cells and, to a lesser extent, by activated mast cells.(2) IL-5 acts on mature eosinophils, leading to proliferation, activation, and differentiation. IL-5 is a critical part of the immune response to helminths. Eosinophils activated by IL-5 will bind, through Fc receptors, to helminths that have been opsonized by IgG or IgA. Elevations in IL-5 may be observed in conditions associated with hypereosinophilia. Hypereosinophilia is most commonly seen in various forms of atopic disease, including urticaria, asthma, allergic bronchopulmonary aspergillosis,

<=1033 pg/mL
and drug allergies. Elevated numbers of eosinophils may also be observed in certain vasculitides, specifically eosinophilic granulomatosis with polyangiitis (EGPA). EGPA is characterized by asthma, pulmonary infiltrates, history of allergies, and hypereosinophilia usually above 1500/mL. Hypereosinophilia may also be observed in certain primary immunodeficiencies (such as Job syndrome), leukemias, and lymphomas. IL-5 is thought to be important in driving eosinophil proliferation in these various conditions. Recently, an advisory committee of the FDA has recommended that mepolizumab, a monoclonal anti-IL-5 antibody, be approved for the treatment of severe eosinophilic asthma in adults. Other IL-5 blocking antibodies (reslizumab and benralizumab) are also in development, with clinical trials designed to determine specific clinical utility.

**Useful For:** Evaluation of patients with disorders known to be associated with hypereosinophilia

**Interpretation:** Elevated concentrations of interleukin-5 (IL-5) may indicate an expanded Th2 (helper T cells, subset 2)-immune response, which may be associated with hypereosinophilia.

**Reference Values:**

< or =1.0 pg/mL

**Clinical References:**


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**Interleukin 6 (IL-6), Plasma**

**Clinical Information:** Interleukin-6 (IL-6) has important roles in both innate and adaptive immunity. IL-6 can be produced by a variety of different cell types, including macrophages, endothelial cells, and T cells. This production can be initiated in response to microbial invasion or other cytokines, such as tumor necrosis factor (TNF). As part of the innate immune system, IL-6 acts on hepatocytes to induce expression of C-reactive protein (CRP), fibrinogen, and serum amyloid A, also known as the acute phase response. Within the adaptive immune response, IL-6 plays a key role in activating antibody-producing B cells to proliferate, leading to an enhanced antibody response. Concentrations of IL-6 are elevated in patients with infection, sepsis, and septicemia. In addition, IL-6 concentrations appear to correlate with severity of sepsis, as defined by clinical and laboratory parameters. Elevations in IL-6 also appear to be associated with more localized infections, such as prosthetic joint infections (PJI). A recent meta-analysis demonstrated that IL-6 had improved diagnostic accuracy for PJI compared to CRP, erythrocyte sedimentation rate (ESR), and white blood cell counts. IL-6 is also elevated in numerous chronic inflammatory disorders, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), and inflammatory bowel disease (IBD). There is evidence that IL-6 is involved in the pathogenesis of certain chronic inflammatory disorders. Tocilizumab, an antibody that blocks IL-6 function by binding to the IL-6 receptor, has been approved for the treatment of RA. In a randomized trial, 50% to 60% of patients receiving tocilizumab and methotrexate showed improvement in clinical signs and symptoms of RA, compared to only 25% in patients receiving methotrexate alone.

**Useful For:** Evaluation of patients with suspected systemic infection Evaluation of patients with suspected localized infection, specifically prosthetic joint infection (PJI) Evaluation of patients with suspected chronic inflammatory disorders, such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, or inflammatory bowel disease

**Interpretation:** Elevated concentrations of Interleukin-6 (IL-6) may indicate an ongoing inflammatory response, and could be consistent with a systemic infection, localized infection, or chronic inflammatory disease.

**Reference Values:**

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 1276

FIL1S 57534  Interleukin-10 (IL-10) Serum
Reference Values:
<2.0 pg/mL

FIL4S 57585  Interleukin-4 (IL-4) Serum
Reference Values:
<2.0 pg/mL

FIL8S 57563  Interleukin-8 (IL-8) Serum
Reference Values:
<57.8 pg/mL

IFBA 9335  Intrinsic Factor Blocking Antibody, Serum
Clinical Information: The cobalamins, also referred to as vitamin B12, are a group of closely related enzymatic cofactors involved in the conversion of methylmalonyl-coenzyme A to succinyl-coenzyme A and in the synthesis of methionine from homocysteine. Vitamin B12 deficiency can lead to megaloblastic anemia and neurological deficits. The latter may exist without anemia, or precede it. Adequate replacement therapy will generally improve or cure cobalamin deficiency. Unfortunately, many other conditions, which require different interventions, can mimic the symptoms and signs of vitamin B12 deficiency. Moreover, even when cobalamin deficiency has been established, clinical improvement may require different dosages or routes of vitamin B12 replacement, depending on the underlying cause. In particular, patients with pernicious anemia (PA), possibly the commonest type of cobalamin deficiency in developed countries, require either massive doses of oral vitamin B12 or parenteral replacement therapy. The reason is that in PA patients suffer from gastric mucosal atrophy, most likely caused by a destructive autoimmune process. This results in diminished or absent gastric acid, pepsin and intrinsic factor (IF) production. Gastric acid and pepsin are required for liberation of cobalamin from binding proteins, while IF binds the free vitamin B12, carries it to receptors on the ileal mucosa, and facilitates its absorption. Most PA patients have autoantibodies against gastric parietal cells or intrinsic factor, with the latter being very specific but only present in approximately 50% of cases. By contrast, parietal cell antibodies are found in approximately 90% of PA patients, but are also found in a significant proportion of patients with other autoimmune diseases, and in approximately 2.5% (4th decade of life) to approximately 10% (8th decade of life) of healthy individuals.

Useful For: Confirming the diagnosis of pernicious anemia

Interpretation: The aim of the work-up of patients with suspected vitamin B12 deficiency is to first confirm the presence of deficiency and then to establish its most likely etiology. Measurement of serum vitamin B12, either preceded or followed by serum methylmalonic acid measurement, is the first step in
diagnosing pernicious anemia (PA). If these tests support deficiency, then intrinsic factor blocking antibody (IFBA) testing is indicated to confirm PA as the etiology. A positive IFBA test supports very strongly a diagnosis of PA. Since the diagnostic sensitivity of IFBA testing for PA is only around 50%, an indeterminate or negative IFBA test does not exclude the diagnosis of PA. In these patients, either PA or another etiology, such as malnutrition, may be present. Measurement of serum gastrin levels will help in these cases. In patients with PA, fasting serum gastrin is elevated to >200 pg/mL in an attempted compensatory response to the achlorhydria seen in this condition. For a detailed overview of the optimal testing strategies in PA diagnosis, see ACASM / Pernicious Anemia Cascade, Serum, and associated Vitamin B12 Deficiency Evaluation in Special Instructions.

Reference Values:
Negative


Iodine, 24 Hour, Urine

Clinical Information: Iodine is an essential element for thyroid hormone production. The measurement of urinary iodine serves as an index of adequate dietary iodine intake.

Useful For: Monitoring iodine excretion rate as an index of daily iodine replacement therapy
Correlating total body iodine load with (131)I-uptake studies in assessing thyroid function

Interpretation: Daily urinary output <90 mcg/specimen suggests dietary deficiency. Values >1,000 mcg/specimen may indicate dietary excess, but more frequently suggest recent drug or contrast media exposure.

Reference Values:
0-15 years: not established
> or =16 years: 93-1,125 mcg/specimen


Iodine, Random, Urine

Clinical Information: Iodine is an essential element for thyroid hormone production. The measurement of urinary iodine serves as an index of adequate dietary iodine intake.

Useful For: Monitoring iodine excretion rate as an index of daily iodine replacement therapy
Correlating total body iodine load with (131)I-uptake studies in assessing thyroid function

Interpretation: Daily urinary output <20 mcg/L suggest dietary deficiency. Values >1,000 mcg/L may indicate dietary excess, but more frequently suggest recent drug or contrast media exposure.

Reference Values:
0-15 years: not established
> or =16 years: 26-705 mcg/L

Iodine, Serum

**Clinical Information:** Iodine is an essential element that is required for thyroid hormone production. The measurement of iodine serves as an index of adequate dietary iodine intake and iodine overload, particularly from iodine-containing drugs such as amiodarone.

**Useful For:** Determination of iodine overload Monitoring iodine levels in individuals taking iodine-containing drugs

**Interpretation:** Values between 80 ng/mL and 250 ng/mL have been reported to indicate hyperthyroidism. Values >250 ng/mL may indicate iodine overload.

**Reference Values:**
40-92 ng/mL


Iodine/Creatinine Ratio, Random, Urine

**Clinical Information:** Iodine is an essential element for thyroid hormone production. The measurement of urinary iodine serves as an index of adequate dietary iodine intake.

**Useful For:** Monitoring iodine excretion rate as an index of daily iodine replacement therapy Correlating total body iodine load with (131)I uptake studies in assessing thyroid function

**Interpretation:** Daily urinary output <70 mcg/g creatinine suggest dietary deficiency. Values >1,000 mcg/g creatinine may indicate dietary excess, but more frequently suggest recent drug or contrast media exposure.

**Reference Values:**
16-40 years: 70-530 mcg/g Creatinine
41-70 years: 70-860 mcg/g Creatinine
>70 years: 70-1,150 mcg/g Creatinine

Reference values have not been established for patients that are <16 years of age.


Iohexol, Plasma

**Clinical Information:** The assessment of glomerular filtration rate (GFR) is an important parameter of renal function utilized by clinicians in the care of patients with varying renal diseases, and for clinical research when precise assessment of renal function is necessary. The GFR is the sum of all the filtration rates of the individual nephrons within the kidney and, as such, reflects the number of functioning nephrons. Plasma concentrations of iohexol can be used for measurement of GFR through multiple plasma iohexol determinations following an intravenous bolus injection of iohexol (plasma disappearance), or following a continuous infusion (or subcutaneous injection) of iohexol when used in conjunction with urine iohexol determinations (urinary clearance; HEXU / Iohexol, Timed Collection, Urine).
Useful For: Determining glomerular filtration rate in plasma specimens

**Interpretation:** Low glomerular filtration rate (GFR) values indicate abnormal renal function, which may be either reversible/transient or irreversible/permanent. GFR tends to decline with age.

**Reference Values:**
Not applicable

**Clinical References:**

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**Iohexol, Timed Collection, Urine**

**Clinical Information:** The assessment of glomerular filtration rate (GFR) is an important parameter of renal function utilized by clinicians in the care of patients with varying renal diseases, and for clinical research when precise assessment of renal function is necessary. The GFR is the sum of all the filtration rates of the individual nephrons within the kidney and, as such, reflects the number of functioning nephrons. Urine concentrations of iohexol can be used for measurement of GFR following a subcutaneous injection of iohexol (plasma disappearance), or during a continuous infusion of iohexol when used in conjunction with plasma iohexol determinations (HEXP / Iohexol, Plasma). The results can be used to determine the clearance of iohexol, which is a measure of GFR.

**Useful For:** Determining glomerular filtration rate in urine specimens

**Interpretation:** Low glomerular filtration rate (GFR) values indicate abnormal renal function, which may be either reversible/transient or irreversible/permanent. GFR tends to decline with age.

**Reference Values:**
Not applicable

**Clinical References:**

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**Ipecac Use Markers**

**Reference Values:**
Therapeutic and toxic ranges have not been established.

Emetine and cephaeline are alkaloids present in ipecac.

Serum emetine levels within 2 hours of a 30 mL dose of ipecac syrup range from 0 - 75.0 ng/mL.

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**Iron and Total Iron-Binding Capacity, Serum**

**Clinical Information:** Ingested iron is absorbed primarily from the intestinal tract and is temporarily stored in the mucosal cells as ferritin (Fe[III]). Ferritin provides a soluble protein shell to encapsulate a complex of insoluble ferric hydroxide-ferric phosphate. On demand, iron is released into the blood by mechanisms that are not clearly understood, to be transported as Fe(III)-transferrin. Transferrin is the primary plasma iron transport protein, which binds iron strongly at physiological pH. Transferrin is generally only 25% to 30% saturated with iron. The additional amount of iron that can be bound is the unsaturated iron-binding capacity (UIBC). The total iron-binding capacity (TIBC) can be indirectly

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determined using the sum of the serum iron and UIBC. Knowing the molecular weight of the transferrin and that each molecule of transferrin can bind 2 atoms of iron, TIBC and transferrin concentration is interconvertible. Percent saturation (100 x serum iron/TIBC) is usually normal or decreased in persons who are iron deficient, pregnant, or are taking oral contraceptive medications. Persons with chronic inflammatory processes, hemochromatosis, or malignancies generally display low transferrin. Serum iron, total iron-binding capacity, and percent saturation are widely used for the diagnosis of iron deficiency. However, serum ferritin is a much more sensitive and reliable test for demonstration of iron deficiency.

**Useful For:** Screening for chronic iron overload diseases, particularly hereditary hemochromatosis

**Interpretation:** In hereditary hemochromatosis, serum iron is usually above 150 mcg/dL and percent saturation is above 60%. In advanced iron overload states, the percent saturation often is above 90%. For more information about hereditary hemochromatosis testing, see Hereditary Hemochromatosis Algorithm in Special Instructions.

**Reference Values:**

- **IRON**
  - Males: 50-150 mcg/dL
  - Females: 35-145 mcg/dL

- **TOTAL BINDING CAPACITY**
  - 250-400 mcg/dL

- **PERCENT SATURATION**
  - 14-50%

**Clinical References:**


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**Iron, Liver Tissue**

**Clinical Information:** Hemosiderosis is the condition of excessive iron accumulation in tissues. Liver is the first organ affected in iron-overload diseases. Transient increases in iron first appear in Kupffer cells. This finding is commonly related to sideroblastic anemia, excessive iron consumption, or chronic alcohol ingestion. Persistent hemosiderosis, as seen in hemochromatosis, causes iron accumulation in hepatocytes, and is usually concentrated in biliary cells. Hereditary hemochromatosis is an autosomal recessive disease with estimated prevalence in the population of 2 in 1,000 in Caucasians, with lower incidence in other races. The gene responsible for hereditary hemochromatosis (HFE) is located on chromosome 6; the majority of hereditary hemochromatosis patients have mutations in this HFE gene. Hereditary hemochromatosis is characterized by an accelerated rate of intestinal iron absorption and progressive iron deposition in various tissues that typically begins to be expressed in the third to fifth decades of life, but may occur in children. The most common presentation is hepatic cirrhosis in combination with hypopituitarism, cardiomyopathy, diabetes, arthritis, or hyperpigmentation. Because of the severe sequelae of this disease if left untreated and recognizing that treatment is relatively simple, early diagnosis before symptoms or signs appear is important. Screening for hemochromatosis is best done by measuring serum iron and transferrin saturation (FEC / Iron and Total Iron-Binding Capacity, Serum). If the serum iron concentration is above 175 mcg/dL and the transferrin saturation is above 55%, analysis of serum ferritin concentration (FERR / Ferritin, Serum) is indicated. A ferritin concentration above 400 ng/mL is suggestive of hemochromatosis, but also can indicate other forms of hepatocyte injury such as alcoholic or viral hepatitis, or other inflammatory disorders involving the liver. HFE analysis (HFE / Hemochromatosis HFE Gene Analysis, Blood) may be used to confirm the clinical diagnosis of hemochromatosis, to diagnose hemochromatosis in asymptomatic individuals with blood tests showing increased iron stores, or for predictive testing of individuals who have a family history of hemochromatosis. The alleles evaluated by HFE gene analysis are evident in approximately 80% of patients with hemochromatosis; a negative report for HFE gene does not rule-out hemochromatosis. In a patient with negative HFE gene testing, elevated iron status for
no other obvious reason, and family history of liver disease, additional evaluation of liver iron concentration is indicated. Diagnosis of hemochromatosis may also be based on biochemical analysis and histologic examination of a liver biopsy. In this assay (FET / Iron Liver Tissue), results are reported as the hepatic iron index (HII) and dry weight of iron. The HII is considered the "gold standard" for diagnosis of hemochromatosis. This test is appropriate when: 
- Serum iron is above 160 mcg/dL
- Transferrin saturation is above 55%
- Ferritin is above 400 ng/mL in males or above 200 ng/mL in females
- HFE gene test is negative for HFE variants

See Hereditary Hemochromatosis Algorithm in Special Instructions.

**Useful For:** Diagnosis of hemochromatosis

**Interpretation:** A hepatic iron concentration above 10,000 mcg/g dry weight is diagnostic for hemochromatosis. Hepatic iron concentrations above 3,000 mcg/g are seen when there is iron overload without cellular injury and cirrhosis. Hepatic iron concentrations greater than the reference range are associated with hemosiderosis, thalassemia, and sideroblastic anemia. Some patients with hepatitis or cirrhosis without significant fibrosis will have hepatic iron concentrations at the top end of normal or just slightly above the normal range. Iron accumulates in the liver normally with aging. The hepatic iron index (HII) normalizes hepatic iron concentration for age. The HII is calculated from the hepatic iron concentration by converting the concentration from mcg/g to mcmol/g dry weight and dividing by years of age. The normal range for HII is less than 1.0.

- Patients with homozygous hemochromatosis have an HII above 1.9.
- Patients with heterozygous hemochromatosis often have an HII ranging from 1.0 to 1.9.
- Patients with hepatitis and alcoholic cirrhosis usually have an HII below 1.0, although a small percentage of patients with alcoholic cirrhosis have an HII in the range of 1.0 to 1.9.

Liver specimens collected from patients with cirrhosis containing a high degree of fibrosis have results near the low end of the reference range, even though they will show significant iron staining in hepatocytes. While it is true that iron accumulates in hepatocytes in advanced alcoholic cirrhosis with fibrosis, there are relatively few hepatocytes compared to other inert (fibrotic) tissue, so the quantitative iron determination, which is expressed as mcg of iron per gram of dry weight tissues, yields a low result. Histologic examination of all tissue specimens should be performed to facilitate correct interpretation. When structural heterogeneity is apparent histologically, variation in measured iron should be anticipated. We have observed, in approximately 2% of cases, a high degree of hepatic heterogeneity that makes quantitation highly variable.

**Reference Values:**

**IRON**
- Males: 200-2,400 mcg/g dry weight
- Females: 400-1,600 mcg/g dry weight

**IRON INDEX**
Reference values have not been established for patients that are <13 years of age.

<1.0 mcmol/g/year (> or =13 years)

**Clinical References:**

**ISPCA 113306**

**ISH Additional (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.
**Islet 1 Immunostain, Technical Component Only**

**Clinical Information:** Islet 1 is a homeobox-gene-related transcription factor involved in the development of the endocrine pancreas. It is composed of 349 amino acids and has a molecular weight of 39 kd. Islet 1 is expressed in subsets of neurons of the adrenal medulla and dorsal root ganglion cell layers in the retina, the pineal gland, and some areas of the brain. In the pancreas, islet 1 is expressed in all endocrine, but not in exocrine, pancreatic cells. The majority of primary and metastatic pancreatic endocrine tumors express islet 1.

**Useful For:** Aids in the identification of endocrine tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a
qualified pathologist.


**IA2**

**Islet Antigen 2 (IA-2) Antibody, Serum**

**Clinical Information:** Islet cell autoantibodies have been known to be associated with type 1 diabetes mellitus for 36 years. In recent years, several autoantigens against which islet antibodies are directed have been identified. These include the tyrosine phosphatase-related islet antigen 2 (IA-2), glutamic acid decarboxylase 65, the zinc transporter ZnT8, and insulin. One or more of these autoantibodies are detected in 96% of patients with type 1 diabetes, and are detectable before clinical onset, as well as in symptomatic individuals. A serological study of 50 type 1 diabetics and 50 control subjects conducted simultaneously across 43 laboratories in 16 countries demonstrated a median sensitivity of 57% and a median specificity of 99% for IA-2 antibody in type 1 diabetes. Prospective studies in relatives of patients with type 1 diabetes have shown that development of 1 or more islet autoantibodies (including IA-2 antibody) provides an early marker of progression to type 1 diabetes. Autoantibody profiles identifying patients destined to develop type 1 diabetes are usually detectable before age 3. In 1 study of relatives seropositive for IA-2 antibody, the risk of developing type 1 diabetes within 5 years was 65.3%. Some patients with type 1 diabetes are initially diagnosed as having type 2 diabetes because of symptom onset in adulthood, societal obesity, and initial insulin-independence. These patients with "latent autoimmune diabetes in adulthood" may be distinguished from those patients with type 2 diabetes by detection of 1 or more islet autoantibodies (including IA-2).

**Useful For:** Clinical distinction of type 1 from type 2 diabetes mellitus. Identification of individuals at risk of type 1 diabetes (including high-risk relatives of patients with diabetes). Prediction of future need for insulin treatment in adult-onset diabetic patients.

**Interpretation:** Seropositivity for IA-2 autoantibody (> 0.02 nmol/L) is supportive of: - A diagnosis of type 1 diabetes - A high risk for future development of diabetes - A current or future need for insulin therapy in patients with diabetes.

**Reference Values:**

< or = 0.02 nmol/L

Reference values apply to all ages.


**FISLC**

**Islet Cell Cytoplasmic Ab, IgG**

**Reference Values:**

< 1:4

Islet cell antibodies (ICAs) are associated with type 1 diabetes (TID), an autoimmune endocrine disorder. ICAs may be present years before the onset of clinical symptoms. To calculate Juvenile Diabetes Foundation (JDF) units: multiply the titer x 5 (1:8  x 5 = 40 JDF Units).
Isoagglutinin Titer, Anti-A, Serum

Clinical Information: Isoagglutinins are antibodies produced by an individual that cause agglutination of RBCs in other individuals. People possess isoagglutinins directed toward the A or B antigen absent from their own RBCs. For example, type B or O individuals will usually possess anti-A. The anti-A is formed in response to exposure to A-like antigenic structures found in ubiquitous non-red cell biologic entities (eg, bacteria). Isoagglutinins present in the newborn are passively acquired from maternal circulation. Such passively acquired isoagglutinins will gradually disappear, and the infant will begin to produce isoagglutinins at 3 to 6 months of age. Isoagglutinin production may vary in patients with certain pathologic conditions. Decreased levels of isoagglutinins may be seen in patients with acquired and congenital hypogammaglobulinemia and agammaglobulinemia. Some individuals with roundworm infections will have elevated levels of anti-A.

Useful For: Evaluation of individuals with possible hypogammaglobulinemia Investigation of suspected roundworm infections

Interpretation: The result is reported as antiglobulin phase, in general representing IgG antibody. The result is the reciprocal of the highest dilution up to 1:1024 at which macroscopic agglutination (1+) is observed. Dilutions above 1:1024 are reported as >1024.

Reference Values: Interpretation depends on clinical setting. No defined reference values.


ISOAGGLUTININ TITER, Anti-B, Serum

Clinical Information: Isoagglutinins are antibodies produced by an individual that cause agglutination of RBCs in other individuals. People possess isoagglutinins directed toward the A or B antigen absent from their own RBCs. For example, type A or O individuals will usually possess anti-B. The anti-B is formed in response to exposure to B-like antigenic structures found in ubiquitous non-red cell biologic entities (eg, bacteria). Isoagglutinins present in the newborn are passively acquired from maternal circulation. Such passively acquired isoagglutinins will gradually disappear, and the infant will begin to produce isoagglutinins at 3 to 6 months of age. Isoagglutinin production may vary in patients with certain pathologic conditions. Decreased levels of isoagglutinins may be seen in patients with acquired and congenital hypogammaglobulinemia and agammaglobulinemia.

Useful For: Evaluation of individuals with possible hypogammaglobulinemia

Interpretation: The result is reported as antiglobulin phase, in general representing IgG antibody. The result is the reciprocal of the highest dilution up to 1:1024 at which macroscopic agglutination (1+) is observed. Dilutions above 1:1024 are reported as >1024.

Reference Values: Interpretation depends on clinical setting. No defined reference values.


Isocitrate Dehydrogenase 1 and 2 (IDH1/IDH2) Mutation Analysis, Tumor

Clinical Information: IDH1 and IDH2 (IDH) genes encode dehydrogenase enzymes that are involved in cellular glucose metabolism and oxidative damage control. IDH mutations, primarily involving codons R132 in IDH1 and R172 in IDH2, result in reduction of the enzyme physiological
activity and gain of a neomorphic ability to generate oncometabolite R(-)-2-hydroxyglutarate, which contribute to tumorigenesis by altering numerous cellular responses, including genome-wide epigenetic changes that characterize the glioma CpG island methylator phenotype (G-CIMP). IDH mutations seem to be an early event in gliomagenesis and have been identified in over 70% of lower-grade (grades II/III) diffuse gliomas and secondary glioblastoma. These mutations are rarely seen in other central nervous system tumors and are not seen in reactive non-neoplastic processes, and define a group of lower and high-grade diffuse gliomas associated with a more favorable prognosis. Assessment of IDH mutation status in central nervous system tumors may assist in tumor classification and provide prognostically relevant information for subgroups of patients with diffuse gliomas. IDH1 and IDH2 gene mutations are also observed in a variety of non-CNS tumor types. Assessment of IDH mutation status may assist in the differential diagnosis of chondroid bone tumors and provide prognostically relevant information in other contexts, such as in the setting of acute myeloid leukemia (AML).

**Useful For:** Supporting a morphological diagnosis of a diffuse glioma Assisting in central nervous system tumor classification Stratifying prognosis of diffuse gliomas Supporting the differential diagnosis of chondroid bone tumors Stratifying prognosis of acute myeloid leukemia

**Interpretation:** An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

**Isocyanate HDI, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the
concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE (kU/L)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


**IMDI 82774 Isocyanate MDI, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE (kU/L)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.

approximately 20 mcg/mL and greater.

Isoniazid is known to have limited stability in biological specimens which may be concentration and storage condition dependent. Negative or lower than expected results should be interpreted with caution.

**IVDA**

**Isovaleryl-CoA Dehydrogenase (IVD) Gene Mutation Analysis (A282V)**

**Clinical Information:** Isovaleric acidemia (IVA) is an autosomal recessive inborn error of leucine metabolism associated with germline mutations of the isovaleryl-CoA dehydrogenase (IVD) gene. Mutations in this gene cause isovaleryl-CoA dehydrogenase (IVD) deficiency. This enzyme defect results in the accumulation of derivatives of isovaleryl-CoA, including free isovaleric acid, 3-OH valeric acid, N-isovalerylglucose, and isovalerylcarnitine. Diagnosis relies primarily on the identification of these metabolites in urine by organic acid and acylglycine analyses, and in plasma by acylcarnitine analysis. Patients with IVA may present with various phenotypes, from the acute, neonatal phenotype to the chronic intermittent phenotype. Typically patients present with fairly nonspecific features including poor feeding and vomiting. During these episodes, a characteristic smell of "dirty socks" may be present. In the past, many patients with neonatal onset died during the first episode, while survivors of acute manifestations often suffered neurological sequelae due to incurred central nervous system damage. Therefore, early diagnosis and treatment is of the utmost importance. Newborn screening for IVA was established to allow for early detection by acylcarnitine analysis and presymptomatic initiation of treatment. This early detection has led to improved prognosis for IVA patients. Molecular follow-up testing for patients with positive newborn screening for IVA has led to the identification of specific mutant alleles. One such mutant allele A282V (historic nomenclature: A282V, current nomenclature: A314V) has been found to be overrepresented in patients detected by newborn screening. Clinical evaluation of patients with the A282V mutant allele suggests that this specific mutant allele may confer a milder clinical phenotype. Accordingly, determination of the patient's genotype with respect to the A282V mutation has implications for patient management and genetic counseling.

**Useful For:** Confirmation of clinical or biochemical diagnosis of isovaleric acidemia Providing prognostic information for patients with isovaleric acidemia

**Interpretation:** An interpretive report will be provided.


**ISPG**

**Ispaghula, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
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<td>6</td>
<td>&gt; or =100</td>
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</tr>
</tbody>
</table>

**Reference values apply to all ages.**


**Itraconazole, Serum**

**Clinical Information:** Itraconazole is a synthetic triazole antifungal drug approved for treatment and prophylaxis of a variety of fungal infections. Its activity results from inhibition of fungal synthesis of ergosterol, an integral component of fungal cell membranes. Concerns about adequate absorption and drug interactions are some of the major indications for therapeutic drug monitoring. Mean oral bioavailability approximates 55% but is highly variable; absorption can be enhanced by food or acidic drinks. Hepatic enzyme inducers can cause low serum itraconazole levels, and coadministration of these drugs has been associated with itraconazole therapeutic failure. Itraconazole therapeutic efficacy is greatest when serum concentrations exceed 0.5 mcg/mL for localized infections, or 1.0 mcg/mL for systemic infections. An active metabolite, hydroxyitraconazole, is present in serum at roughly twice the level of the parent drug. These concentrations refer to analysis by HPLC; quantitation by bioassay results in considerably higher apparent drug measurements, due to reactivity with the active metabolite.

**Useful For:** Verifying systemic absorption of orally administered itraconazole. The test is indicated in patients with life-threatening fungal infections and in patients considered at risk for poor absorption or rapid clearance of itraconazole.

**Interpretation:** A lower cutoff concentration has not been defined that applies in all cases. The serum concentration must be interpreted in association with other variables, such as the nature of the infection, the specific microorganism, and minimal inhibitory concentration (MIC) results, if available. Localized infections are more likely to respond when serum itraconazole is >0.5 mcg/mL (by HPLC); systemic infections generally require drug concentrations >1.0 mcg/mL.

**Reference Values:**

<table>
<thead>
<tr>
<th>ITRACONAZOLE (TROUGH)</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.5 mcg/mL</td>
<td>(localized infection)</td>
</tr>
</tbody>
</table>
HYDROXYITRACONAZOLE

No therapeutic range established; activity and serum concentration are similar to parent drug.


JCHAIN

J-Chain Immunostain, Technical Component Only

Clinical Information: J-chain is a small, glycopeptide of 15 kD that is structurally unrelated to heavy or light chains. It serves to structurally link the immunoglobulin components of polymeric immunoglobulins IgA and IgM, and appears to play a role in secretion of antibodies at mucosal sites. B cells in the germinal center express J-chain at an early stage of differentiation, with the expression persisting in the plasma cells destined to produce IgA or IgM.

Useful For: Classification of lymphomas

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


JACK

Jack Fruit, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to
identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>50.0-99.9</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


JAK2F 64980

**JAK2 (9p24.1) Rearrangement for Hematologic Disorders, FISH**

**Clinical Information:** The JAK2 gene is a protein tyrosine kinase involved in cytokine signaling. Chromosomal translocations involving JAK2 can lead to the formation of chimeric oncoproteins in hematologic malignancies. Rearrangements involving 9p24.1 are typically aggressive and rare abnormalities seen in various hematologic diseases. JAK2 inhibitors are one of the only therapy options besides a stem cell transplant for JAK2 rearrangements.

**Useful For:** Providing diagnostic information and helping to determine whether a targeted JAK2 inhibitor could be useful for therapy

**Interpretation:** A positive result is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result suggests rearrangement of the JAK2 locus. A negative result suggests no rearrangement of the JAK2 gene region at 9p24.1.

**Reference Values:**
An interpretive report will be provided.


JAKXB 89189

**JAK2 Exon 12 and Other Non-V617F Mutation Detection, Blood**

**Clinical Information:** DNA sequence mutations in the Janus kinase 2 gene (JAK2) are found in the hematopoietic cells of several myeloproliferative neoplasms (MPNs), most frequently polycythemia vera (close to 100%), essential thrombocythemia (approximately 50%), and primary myelofibrosis (approximately 50%). Mutations in JAK2 have been reported at much lower frequency in other MPNs, chronic myelomonocytic leukemia and mixed MPN/myelodysplastic syndromes, but essentially never in chronic myelogenous leukemia (CML), reactive cytoxes, or normal patients. Mutations are believed to cause constitutive activation of the JAK2 protein, which is an intracellular tyrosine kinase important for signal transduction in many hematopoietic cells. Since it is often difficult to distinguish reactive conditions from the non-CML MPNs, identification of a JAK2 mutation has diagnostic value. Potential prognostic significance of JAK2 mutation detection in chronic myeloid disorders has yet to be clearly established. The vast majority of JAK2 mutations occur as base pair 1849 in the gene, resulting in a JAK2 V617F protein change. In all cases being evaluated for JAK2 mutation status, the initial test that should be ordered is JAK2B / JAK2 V617F Mutation Detection, Blood, a sensitive assay for detection
of the mutation. However, if no JAK2 V617F mutation is found, further evaluation of JAK2 may be clinically indicated. Over 50 different mutations have now been reported within exons 12 through 15 of JAK2 and essentially all of the non-V617F mutations have been identified in polycythemia vera. These mutations include point mutations and small insertions or deletions. Several of the exon 12 mutations have been shown to have biologic effects similar to those caused by the V617F mutation such that it is currently assumed other nonpolymorphic mutations have similar clinical effects. However, research in this area is ongoing. This assay for non-V617F/alternative JAK2 mutations is designed to obtain the sequence for JAK2 exons 12 through the first 90% of exon 15, which spans the region containing all mutations reported to date.

**Useful For:** Second-order testing to aid in the distinction between a reactive cytosis and a myeloproliferative neoplasm, particularly when a diagnosis of polycythemia is being entertained; for use with blood specimens

**Interpretation:** The results will be reported as 1 of 2 states: 1. Negative for JAK2 mutation 2. Positive for JAK2 mutation. If the result is positive, a description of the mutation at the nucleotide level and the altered protein sequence is reported. Positive mutation status is highly suggestive of a myeloproliferative neoplasm, but must be correlated with clinical and other laboratory features for a definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative or other neoplasm.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

**JAK2 Exon 12 and Other Non-V617F Mutation Detection, Bone Marrow**

**Clinical Information:** DNA sequence mutations in the Janus kinase 2 gene (JAK2) are found in the hematopoietic cells of several myeloproliferative neoplasms (MPN), most frequently polycythemia vera (close to 100%), essential thrombocytosis (approximately 50%), and primary myelofibrosis (approximately 50%). Mutations in JAK2 have been reported at much lower frequency in other MPN, chronic myelomonocytic leukemia and mixed MPN/myelodysplastic syndromes, but essentially never in chronic myelogenous leukemia (CML), reactive cytoses, or normal patients. Mutations are believed to cause constitutive activation of the JAK2 protein, which is an intracellular tyrosine kinase important for signal transduction in many hematopoietic cells. Since it is often difficult to distinguish reactive conditions from the non-CML MPN, identification of a JAK2 mutation has diagnostic value. Potential prognostic significance of JAK2 mutation detection in chronic myeloid disorders has yet to be clearly established. The vast majority of JAK2 mutations occur as base pair 1849 in the gene, resulting in a JAK2 V617F protein change. In all cases being evaluated for JAK2 mutation status, the initial test that should be ordered is JAK2M / JAK2 V617F Mutation Detection, Bone Marrow, a sensitive assay for detection of the mutation. However, if no JAK2 V617F mutation is found, further evaluation of JAK2 may be clinically indicated. Over 50 different mutations have now been reported within exons 12 through 15 of JAK2 and essentially all of the non-V617F mutations have been identified in polycythemia vera. These mutations include point mutations and small insertions or deletions. Several of the exon 12 mutations have been shown to have biologic effects similar to those caused by the V617F mutation such that it is currently assumed other nonpolymorphic mutations have similar clinical effects. However, research in this area is ongoing. This assay for non-V617F/alternative JAK2 mutations is designed to obtain the sequence for JAK2 exons 12 through the first 90% of exon 15, which spans the region containing all mutations reported to date.

**Useful For:** Second-order testing to aid in the distinction between a reactive cytosis and a myeloproliferative neoplasm, particularly when a diagnosis of polycythemia is being entertained; for use with bone marrow specimens.
**Interpretation:** The results will be reported as 1 of 2 states: 1. Negative for JAK2 mutation 2. Positive for JAK2 mutation If the result is positive, a description of the mutation at the nucleotide level and the altered protein sequence is reported. Positive mutation status is highly suggestive of a myeloproliferative neoplasm, but must be correlated with clinical and other laboratory features for a definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative or other neoplasm.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**JAK2 Exon 12-15 Sequencing, Polycythemia Vera Reflex**

**Clinical Information:** The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. The JAK2 V617F is located in exon 14 and present in 50% to 60% of primary myelofibrosis and essential thrombocytopenia, and 95% to 98% of polycythemia vera (PV). In the rest of the polycythemia vera cases, over 50 different mutations have been reported within exons 12 through 15 of JAK2 and essentially all of the non-V617F JAK2 mutations have been identified in polycythemia vera. These mutations include point mutations and small insertions or deletions. Several of the exon 12 mutations have been shown to have biologic effects similar to those caused by the V617F mutation such that it is currently assumed other nonpolymorphic mutations have similar clinical effects. However, some mutations may not be well characterized and requires further clinical and research evaluation.

**Useful For:** Aiding in the distinction between the myeloproliferative neoplasm polycythemia vera (PV) and other secondary erythrocytosis Evaluating for mutations within exons 12 to 15 of JAK2 in an algorithmic process as part of PVJAK / Polycythemia Vera, JAK2 V617F with Reflex to JAK2 Exon 12-15, Sequencing for Erythrocytosis

**Interpretation:** The results will be reported as 1 of the 3 following states: -Positive for JAK2 V617F mutation -Positive for JAK2 mutation (other than V617F) -Negative for JAK2 mutations If the result is positive, a description of the mutation at the nucleotide level and the altered protein sequence are reported. A positive mutation status is highly suggestive of a myeloid neoplasm and may support a diagnosis of polycythemia vera in the appropriate clinical setting. Correlation with clinicopathologic findings and other laboratory results is necessary in all cases. A negative mutation status makes a diagnosis of polycythemia vera highly unlikely, although it does not completely exclude this possibility, other myeloproliferative neoplasms or other neoplasms.

**Reference Values:**
Only orderable as a reflex. For more information, see PVJAK / Polycythemia Vera, JAK2 V617F with Reflex to JAK2 Exon 12-15, Sequencing for Erythrocytosis.

**Clinical References:**
JAK2 V617F Mutation Detection, Blood

Clinical Information: The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR-ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide mutation in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). This mutation is identified overall in approximately two-thirds of all MPN,(1-3) but the prevalence varies by MPN subtype. The JAK2 V617F is present in 95% to 98% of polycythemia vera, 50% to 60% of primary myelofibrosis, and 50% to 60% of essential thrombocytopenia. It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome.(4) This mutation is not seen in chronic myelogenous leukemia (CML) or in reactive conditions with elevated blood counts. Detection of the JAK2 V617F is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate absence of a MPN. Other important molecular markers in BCR-ABL1-negative MPN include CALR exon 9 mutation (20%-30% of PMF and ET) and MPL exon 10 mutation (5%-10% of PMF and 3%-5% of ET).(5-9) Mutations in JAK2, CALR, and MPL are essentially mutually exclusive.

Useful For: Aiding in the distinction between a reactive blood cytosis and a chronic myeloproliferative disorder in blood specimens

Interpretation: The results will be reported as 1 of the 2 states: -Negative for JAK2 V617F mutation -Positive for JAK2 V617F mutation Positive mutation status is highly suggestive of a myeloid neoplasm, but must be correlated with clinical and other laboratory features for definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative neoplasm or other neoplasm. Results below the laboratory cutoff for positivity are of unclear clinical significance at this time.

Reference Values:
An interpretive report will be provided.


JAK2 V617F Mutation Detection, Bone Marrow

Clinical Information: The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR-ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide mutation in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). This mutation is identified overall in approximately two-thirds of all MPN,(1-3) but the prevalence varies by MPN subtype. The JAK2 V617F is present in 95% to 98% of polycythemia vera, 50% to 60% of primary myelofibrosis (PMF), and 50% to 60% of essential

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
thrombocythemia (ET). It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome.(4) This mutation is not seen in chronic myelogenous leukemia (CML) or in reactive conditions with elevated blood counts. Detection of the JAK2 V617F is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate absence of a MPN. Other important molecular markers in BCR-ABL1-negative MPN include CALR exon 9 mutation (20%-30% of PMF and ET) and MPL exon 10 mutation (5%-10% of PMF and 3%-5% of ET). Mutations in JAK2, CALR, and MPL are essentially mutually exclusive.

Useful For: Aiding in the distinction between a reactive blood cytosis and a chronic myeloproliferative disorder in bone marrow specimens

Interpretation: The results will be reported as 1 of the 2 states: -Negative for JAK2 V617F mutation -Positive for JAK2 V617F mutation Positive mutation status is highly suggestive of a myeloid neoplasm, but must be correlated with clinical and other laboratory features for definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative neoplasm or other neoplasm. Results below the laboratory cutoff for positivity are of unclear clinical significance at this time.

Reference Values:
An interpretive report will be provided.


JAK2 V617F Mutation Detection, Varies

Clinical Information: The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR-ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide mutation in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). This mutation is identified overall in approximately two-thirds of all MPN,(1-3) but the prevalence varies by MPN subtype. The JAK2 V617F is present in 95% to 98% of polycythemia vera, 50% to 60% of primary myelofibrosis (PMF), and 50% to 60% of essential thrombocythemia (ET). It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome.(4) This mutation is not seen in chronic myelogenous leukemia (CML) or in reactive conditions with elevated blood counts. Detection of the JAK2 V617F is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate absence of a MPN. Other important molecular markers in BCR-ABL1-negative MPN include CALR exon 9 mutation (20%-30% of PMF and ET) and MPL exon 10 mutation (5%-10% of PMF and 3%-5% of ET). Mutations in JAK2, CALR, and MPL are essentially mutually exclusive.

Useful For: Aiding in the distinction between a reactive blood cytosis and a chronic myeloproliferative disorder in extracted DNA specimens

Interpretation: The results will be reported as 1 of the 2 states: -Negative for JAK2 V617F mutation -Positive for JAK2 V617F mutation Positive mutation status is highly suggestive of a myeloid neoplasm, but must be correlated with clinical and other laboratory features for a definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative neoplasm or other neoplasm. Results below the laboratory cutoff for positivity are of unclear clinical significance at this time.
time.

Reference Values:
An interpretive report will be provided.


Jalapeno/Chipotle (Capsicum annuum) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Japanese Cedar, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Japanese Millet, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Clinical Information: JC Virus is the cause of Progressive multifocal Leukoencephalopathy (PML), a severe demyelinating disease of the central nervous system. PML is a particular concern for individuals infected with the human immunodeficiency virus. Quantification of JC virus DNA is based upon the real-time PCR amplification and detection of JCV genomic DNA. The quantitative range of this assay is 500-35,000,000 JCV DNA copies/mL.

Reference Values:
<500 copies/mL

JC Virus Detection by In Situ Hybridization

Clinical Information: JC virus (JCV) is the etiologic agent of progressive multifocal leukoencephalopathy (PML), a rare, demyelinating, fatal disorder of the central nervous system that occurs on a background of immune deficiency. PML is an infrequent complication of a wide variety of conditions, including lymphoproliferative disorders (Hodgkin disease, chronic lymphocytic leukemia), sarcoidosis, tuberculosis, and AIDS.

Useful For: Confirming a clinical and histopathologic diagnosis of progressive multifocal leukoencephalopathy

Interpretation: This test, when not accompanied by a pathology consultation request, will be answered as either positive or negative. If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test.

Clinical References:

JC Virus, Molecular Detection, PCR, Spinal Fluid

Clinical Information: JC virus (JCV), a member of the genus Polyomavirus, is a small nonenveloped DNA-containing virus. Primary infection occurs in early childhood, with a prevalence of greater than 80%. The virus is latent but can reactivate in immunosuppressed patients, especially those with AIDS. JCV is recognized as the etiologic agent of progressive multifocal leukoencephalopathy (PML), a fatal demyelinating disease of the central nervous system.(2,3) Histologic examination of brain biopsy tissue may reveal characteristic pathologic changes localized mainly in oligodendrocytes and astrocytes. Detection of JCV DNA by PCR (target gene, large T antigen) in the cerebrospinal fluid specimens of patients with suspected PML infection has replaced the need for biopsy tissue for laboratory diagnosis.(4) Importantly, the PCR test is specific with no cross-reaction with BK virus, a closely related polyomavirus.

Useful For: Aids in diagnosing progressive multifocal leukoencephalopathy due to JC virus (JCV)
This test is not to be used as a diagnostic tool for Creutzfeldt-Jakob disease (CJD).

Interpretation: Detection of JC virus (JCV) DNA supports the clinical diagnosis of progressive multifocal leukoencephalopathy due to JCV.

Reference Values:
Negative

Jo 1 Antibodies, IgG, Serum

Clinical Information: Jo 1 (histidyl tRNA synthetase) is a member of the amino acyl-tRNA synthetase family of enzymes found in all nucleated cells. Jo 1 antibodies in patients with polymyositis bind to conformational epitopes of the enzyme protein and inhibit its catalytic activity in vitro.(1) Jo 1 antibodies are a marker for the disease polymyositis, and occur most commonly in myositis patients who also have interstitial lung disease. The antibodies occur in up to 50% of patients with interstitial pulmonary fibrosis and symmetrical polyarthritis.(2) See Connective Tissue Disease Cascade (CTDC) in Special Instructions.

Useful For: Evaluating patients with signs and symptoms compatible with a connective tissue disease, especially those patients with muscle pain and limb weakness, concomitant pulmonary signs and symptoms, Raynaud phenomenon, and arthritis

Interpretation: A positive result for Jo 1 antibodies is consistent with the diagnosis of polymyositis and suggests an increased risk of pulmonary involvement with fibrosis in such patients.

Reference Values:
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.


Johnson Grass, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
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Reference values apply to all ages.


**June Grass, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.


FWJR 57953  Juniper Western (Juniperus occidentalis) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values: <0.35 kU/L

FQFKL 57294  Kappa and Lambda Free Light Chains (Bence Jones Protein), Quantitative, Urine

Interpretation: Total urinary protein is determined nephelometrically by adding the albumin and Kappa and/or Lambda light chains. This value may not agree with the total protein as determined by chemical methods, which characteristically underestimate urinary light chains.

Reference Values:
Total Protein: 10-140 mg/d
Albumin, Urine: Detected
Alpha-1, Urine: None Detected
Alpha-2, Urine: None Detected
Urine Beta Globulins: None Detected
Gamma, Urine: None Detected
Free Urinary Kappa Light Chains: 0.14-2.42 mg/dL
Free Urinary Kappa Excretion/Day: by report
Free Urinary Lambda Light Chains: 0.02-0.67 mg/dL
Free Urinary Lambda Excretion/Day: by report
Free Urinary Kappa/Lambda Ratio: 2.04-10.37 (ratio)
IFE Interpretation: by report

KLISH 70615  Kappa and Lambda Light Chain mRNA, In Situ Hybridization (ISH) Technical Component Only

Clinical Information: Restricted expression of immunoglobulin light chains can help support a diagnosis of a plasmacytic neoplasm.

Useful For: Aids in diagnosing plasma cell neoplasms

Interpretation: The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.
**Clinical References:**

**Kappa Light Chain (KappaC) Immunostain, Technical Component Only**

**Clinical Information:** Kappa or lambda immunoglobulin light chains pair with immunoglobulin heavy chains to form complete immunoglobulin molecules. These proteins serve as receptors for antigens in B-lymphocytes and are the secretory products of plasma cells, forming the humoral arm of the immune system. Because individual B cells or plasma cells synthesize immunoglobulin containing either kappa or lambda light chains, but not both, immunoperoxidase stains for light chains can be applied to lymphocyte and plasma cell populations as a marker of clonality and B-cell lineage.

**Useful For:** A marker of clonality and B-cell lineage

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**KappaLambda IHC (Bill Only)**

**Reference Values:**
This test is for billing purposes only. This is not an orderable test.

**Keratan Sulfate Quantitative, Urine**

**Clinical Information:** The mucopolysaccharidoses (MPS) are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAG, also called mucopolysaccharides). Undegraded or partially degraded GAG are stored in lysosomes and excreted in the urine. Accumulation of GAG in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in MPS disorders. There are 11 known enzyme deficiencies that result in MPS. Mucopolysaccharidosis IV (Morquio syndrome) is caused by defective degradation of keratan sulfate due to deficiency of either N-acetylgalactosamine 6-sulfatase in MPS IVA or of beta-galactosidase in MPS IVB. Keratan sulfate, and also chondroitin-6-sulfate in the case of MPS IVA, accumulates in the cells and the excess is excreted in the urine. Common clinical features of Morquio A and B include short-trunk dwarfism, a skeletal (spondyloepiphyseal) dysplasia distinct from...
that in the other MPS, corneal clouding, dental anomalies, cardiac lesions, hepatomegaly, and normal intelligence. Severity varies widely in both types although, is generally thought to be more mild in Morquio B. Estimates of the incidence of MPS IVA syndrome range from 1 in 200,000 to 1 in 300,000 live births and of MPS IVB, about 1 in 250,000 live births. Enzyme replacement therapy (ERT) is available for Morquio A; however, for Morquio B, ERT is supportive only. ERT has been shown to decrease the level of keratan sulfate in the urine in Morquio A patients; however, correlation to therapeutic efficacy remains controversial.

**Useful For:** Monitoring the pharmacodynamic effects of enzyme replacement therapy for Morquio A (MPS IVA)

**Interpretation:** A single numeric value is reported. Patient outcomes cannot be correlated to levels of urinary keratan sulfate.

**Reference Values:**
- 0-12 months: \(< =2.50\) mg/mmol creatinine
- 13-24 months: \(< =2.00\) mg/mmol creatinine
- 25 months-4 years: \(< =1.50\) mg/mmol creatinine
- 5-10 years: \(< =1.00\) mg/mmol creatinine
- 11-18 years: \(< =0.80\) mg/mmol creatinine
- \(> 18\) years: \(< =0.50\) mg/mmol creatinine


**KRT34**

**Keratin (34BE12) Immunostain, Technical Component Only**

**Clinical Information:** Keratin 34 beta E12 (sometimes referred to as Keratin 903) is a monoclonal antibody that reacts with high-molecular-weight cytokeratin. In normal prostate, reactivity for keratin 34BE12 can be seen in the basal layer of prostatic glands in a membranous/cytoplasmic pattern. It is most useful as a basal cell-specific marker in the prostate, and shows loss of staining around glands of prostate cancer, which do not have a basal cell layer.

**Useful For:** Aids in the identification of cells expressing high-molecular-weight cytokeratin

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Keratin (AE1/AE3) Immunostain, Technical Component Only

**Clinical Information:** Keratin clone AE1/AE3 is a broad spectrum cytokeratin antibody that reacts with many low- and high-molecular weight-keratins in a filamentous or membrane pattern in the epithelium of most organs. Diagnostically, antikeratin antibodies are usually applied as part of a panel to determine cell lineage of poorly differentiated malignant tumors.

**Useful For:** Aids in the identification of cells expressing a broad spectrum of cytokeratins (low- and high-molecular-weight keratins)

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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Keratin (CAM 5.2) Immunostain, Technical Component Only

**Clinical Information:** The keratin antibody clone CAM 5.2 reacts with the low-molecular-weight (LMW) cytokeratins CK8 and CK7. All simple (one-layered, polar) epithelial cells contain the paired CK8 and CK18, representing the primary (constitutive) CKs of simple epithelia. These LMW CKs are the only CKs found in some simple epithelium (hepatocytes, pancreatic acini, most endocrine cells and proximal renal tubules). CAM 5.2 reacts with cells in a filamentous pattern within the cytoplasm.

**Useful For:** Aids in the identification of cells expressing low-molecular-weight cytokeratins (CK7 and CK8)

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Keratin (OSCAR) Immunostain, Technical Component Only

Clinical Information: The OSCAR cytokeratin antibody covers a wide spectrum of molecular weights; similar in expression pattern to CAM5.2, with greater coverage of high-molecular-weight range (e.g., squamous epithelium). In normal tonsil, the squamous epithelium shows strong staining, and fibroblastic reticulum cells in interfollicular regions show weaker staining. Diagnostically, antikeratin antibodies are usually applied as part of a panel to determine cell lineage of poorly differentiated malignant tumors.

Useful For: Aids in determining primary site in carcinomas of unknown origin

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Keratin 19 (KRT19) Immunostain, Technical Component Only

Clinical Information: Cytokeratin19 (KRT19) is a low-molecular-weight cytoskeletal protein expressed in simple epithelium, transitional epithelium, and a few complex epithelia (myoepithelium, basal epithelium). Anti-KRT19 is useful in carcinomas with ductal or glandular differentiation.

Useful For: Aids in the identification of cells expressing low-molecular-weight cytokeratin (KRT19)

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


KRT20

**Keratin 20 (KRT20) Immunostain, Technical Component Only**

**Clinical Information:** Cytokeratin 20 stains the cytoplasm of epithelial cells in a granular and/or filamentous pattern, or may appear membrane associated (cytoskeletal) with expression primarily restricted to the epithelium of the lower gastrointestinal tract, urothelium, and Merkel-cells. When used together, Cytokeratin 7 and Cytokeratin 20 may be useful as an aid in determining primary site in carcinomas of unknown origin. Cytokeratin 20 is usually positive in colon carcinomas.

**Useful For:** Aids in determining the primary site in carcinomas of unknown origin

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

KRT56

**Keratin 5/6 (KRT5/6) Immunostain, Technical Component Only**

**Clinical Information:** Keratin 5/6 is a cocktail of high-molecular-weight keratins. Squamous epithelium of normal skin stains in a cytoplasmic pattern with Keratin 5/6. Keratin 5/6 is usually positive in mesotheliomas, and negative in adenocarcinomas, making it useful in separating mesotheliomas from pulmonary adenocarcinomas.

**Useful For:** Aids in the identification of cells expressing high-molecular-weight cytokeratin

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.
KRT7

70488

**Keratin 7 (KRT7) Immunostain, Technical Component Only**

**Clinical Information:** Keratin 7 (KRT7) stains the cytoplasm of epithelial cells in a granular and/or filamentous pattern, or may appear membrane associated (cytoskeletal). In normal tissues, KRT7 is found in a large number of cell types including many ductal and glandular epithelia (biliary and pancreatic ducts, lung alveoli, breast, ovary, endometrium, renal collecting ducts, urothelium, thyroid, placental trophoblasts, and mesothelium). When used together, KRT7 and KRT20 may be useful as an aid in determining primary site in carcinomas of unknown origin.

**Useful For:** Aids in determining primary site in carcinomas of unknown origin

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

KETAX

62730

**Ketamine and Metabolite Confirmation, Chain of Custody, Urine**

**Clinical Information:** Ketamine has been used in the United States as an anesthetic induction agent since 1972. The drug acts by noncompetitive antagonism of the N-methyl-D-aspartate (NMDA)-type glutamate receptors.(1,2) Ketamine has become a popular street drug because of its hallucinogenic effects.(3) Ketamine has a half-life of 3 to 4 hours, and is metabolized to norketamine.(3) The effects from ketamine last from 1 to 5 hours, and ketamine and/or norketamine can be detected in the urine for a period of 1 to 2 days following use.(4) Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection and confirmation of ketamine use Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with
testing the specimen at all times; this control implies that the opportunity for specimen tampering would
be limited.

**Interpretation:** The presence of ketamine and/or norketamine >25 ng/mL is a strong indicator that the
patient has used ketamine.

**Reference Values:**
Negative

Fab therapy and renal dysfunction on the disposition of total and free digoxin. Ann Intern Med

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**KETAU 89443**

**Ketamine and Metabolite Confirmation, Urine**

**Clinical Information:** Ketamine has been used in the United States as an anesthetic induction agent
since 1972. The drug acts by noncompetitive antagonism of the N-methyl-D-aspartate (NMDA)-type
glutamate receptors.(1,2) Ketamine has become a popular street drug because of its hallucinogenic
effects.(3) Ketamine has a half-life of 3 to 4 hours, and is metabolized to norketamine.(3) The effects
from ketamine last from 1 to 5 hours, and ketamine and norketamine can be detected in the urine for a
period of 1 to 2 days following use.(4)

**Useful For:** Detection and confirmation of ketamine use

**Interpretation:** The presence of ketamine or norketamine levels above 25 ng/mL is a strong indicator
that the patient has used ketamine.

**Reference Values:**
Negative

Fab therapy and renal dysfunction on the disposition of total and free digoxin. Ann Intern Med

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**FKMS 57857**

**Ketamine and Metabolite Screen, Serum/Plasma**

**Reference Values:**
Reporting limit determined each analysis
Units: ng/mL

Ketamine:
Synonyms: Ketalar

Reported levels during anesthesia: 500-6,500 ng/mL

Norketamine:
Synonyms: Ketamine Metabolite

The intravenous administration of 2 mg/kg of Ketamine followed by continuous infusion of 41
mcg/kg/minute produced an average steady-state plasma concentration of 2,200 ng Ketamine/mL and an
average peak Norketamine level of 1,050 ng/mL which occurred near the end of the 3 hour infusion.
**Ketoconazole, Serum/Plasma**

**Reference Values:**
Reporting limit determined each analysis

Peak plasma levels of 5.4 +/- 1.7 mcg/mL occurred at approximately 1 hour following a single 200 mg dose and peak plasma levels of 22 +/- 3 mcg/mL occurred at approximately 2 hours following a single 800 mg dose of ketoconazole.

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**Ki-67 (MIB-1) Immunostain, Technical Component Only**

**Clinical Information:** Ki-67 (antibody clone MIB-1), is a nuclear protein playing a pivotal role in maintaining cell proliferation. Ki-67 is present in all non-G0 phases of the cell cycle. Beginning in the mid-G1, the level increases through S and G2 to reach a peak in M phase. In the end of M phase, it is rapidly catabolized. Ki-67 has been employed as a marker of proliferation and, hence, prognosis in neoplasms of many types, such as malignant lymphomas, prostatic and breast adenocarcinomas, astrocytic neoplasms, and soft tissue neoplasms.

**Useful For:** A marker of proliferation in neoplasms

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**Ki-67(MIB-1), Breast, Quantitative Immunohistochemistry, Automated**

**Clinical Information:** Ki-67 (MIB-1 clone) is a monoclonal antibody that reacts with cells undergoing DNA synthesis by binding to the Ki-67 antigen, a marker known to be expressed only in proliferating cells. By measuring the amount of tumor cells expressing Ki-67, an estimate of DNA synthesis can be determined. Studies suggest that Ki-67 (MIB-1) analysis of paraffin-embedded tissue specimens may provide useful prognostic information in various tumor types.

**Useful For:** Determining proliferation of tumor cells in paraffin-embedded tissue blocks from
patients diagnosed with breast carcinoma

**Interpretation:** Results will be reported as a percentage of tumor cells staining positive for Ki-67 (MIB-1). Quantitative Ki-67 (MIB-1) results should be interpreted within the clinical context for which the test was ordered. The scoring method using the Aperio digital pathology system was developed and validated in the Molecular Anatomic Pathology Laboratory, Department of Laboratory Medicine and Pathology, Mayo Clinic (see Method Description).

**Reference Values:**
Varies by tumor type; values reported from 0% to 100%


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**Ki-67(MIB-1), Gastrointestinal/Pancreatic Neuroendocrine Tumors, Quantitative Immunohistochemistry, Automated**

**Clinical Information:** Ki-67(MIB-1 clone) is a monoclonal antibody that reacts with cells undergoing DNA synthesis by binding to the Ki-67 antigen, a marker known to be expressed only in proliferating cells. By measuring the amount of tumor cells expressing Ki-67, an estimate of DNA synthesis can be determined. Studies suggest that Ki-67(MIB-1) analysis of paraffin-embedded tissue specimens may provide useful prognostic information in various tumor types.

**Useful For:** Determining proliferation of tumor cells in paraffin-embedded tissue blocks from patients diagnosed with neuroendocrine tumors of the pancreas or gastrointestinal tract including metastases

**Interpretation:** Results will be reported as a percentage of tumor cells staining positive for Ki-67(MIB-1). Quantitative Ki-67(MIB-1) results should be interpreted within the clinical context for which the test was ordered.

**Reference Values:**
Varies by tumor type; values reported from 0% to 100%


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**Ki-67(MIB-1), Gastrointestinal/Pancreatic Neuroendocrine Tumors, Quantitative Immunohistochemistry, Manual**

**Clinical Information:** Ki-67(MIB-1 clone) is a monoclonal antibody that reacts with cells undergoing DNA synthesis by binding to the Ki-67 antigen, a marker known to be expressed only in proliferating cells. By measuring the amount of tumor cells expressing Ki-67, an estimate of DNA synthesis can be determined. Studies suggest that Ki-67(MIB-1) analysis of paraffin-embedded tissue specimens may provide useful prognostic information in various tumor types.

**Useful For:** Determining proliferation of tumor cells in paraffin-embedded tissue blocks from patients diagnosed with neuroendocrine tumors of the pancreas or gastrointestinal tract including metastases
**Interpretation:** Results will be reported as a percentage of tumor cells staining positive for Ki-67(MIB-1). Semi-quantitative Ki-67(MIB-1) results should be interpreted within the clinical context for which the test was ordered.

**Reference Values:**
This is not an orderable test. Order PATHC / Pathology Consultation. The consultant will determine the need for special stains.

Varies by tumor type; values reported from 0% to 100%

**Clinical References:**
5. Pathology and Genetics Tumours of Endocrine Organs. Edited by RA DeLellis, RV Lloyd, PU Heitz, C Eng. IARC Press, 2004

**Ki67 + Melan A Immunostain, Technical Component Only**

**Clinical Information:** Ki-67 (clone MIB-1) is a nuclear protein (detected by the chromogen DAB) playing a pivotal role in maintaining cell proliferation. Ki-67 is present in late G1-, S-, M-, and G2-phases of the cell cycle. Cells in the G0 (quiescent) phase are negative for this protein. Melan-A or melanoma antigen recognized by T cells (MART-1) (detected by the chromogen Fast Red) is expressed in the cytoplasm of melanocytes. It is a sensitive and specific marker for the diagnosis of melanoma. Melan A is also found in other tumors of melanocytic origin such as clear cell sarcoma, melanotic neurofibroma, melanotic schwannoma, as well as in perivascular epithelioid cell tumor. Melan A (clone A103) cross-reacts with steroid hormone-producing cells and tumors. Consequently, adrenocortical adenomas/carcinomas and sex cord-stromal tumors of the ovary and testis may exhibit staining.

**Useful For:** Ki67 is a marker of proliferation in neoplasms Melan A aids in the identification of melanoma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
**Ki67 Breast IHC Manual**

**Clinical Information:** Ki-67 (MIB-1 clone) is a monoclonal antibody that reacts with cells undergoing DNA synthesis by binding to the Ki-67 antigen, a marker known to be expressed only in proliferating cells. By measuring the amount of tumor cells expressing Ki-67, an estimate of DNA synthesis can be determined. Studies suggest that Ki-67 (MIB-1) analysis of paraffin-embedded tissue specimens may provide useful prognostic information in various tumor types.

**Useful For:** Determining proliferation of tumor cells in paraffin-embedded tissue blocks from patients diagnosed with breast carcinoma

**Interpretation:** Results will be reported as a percentage of tumor cells staining positive for Ki-67(MIB-1). Quantitative Ki-67 (MIB-1) results should be interpreted within the clinical context for which the test was ordered.

**Reference Values:**
This is not an orderable test. Order PATHC / Pathology Consultation. The consultant will determine the need for special stains.

Varies by tumor type; values reported from 0% to 100%

**Clinical References:**

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**Kidney Bean (Red), IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
</tr>
</tbody>
</table>
Kidney Stone Analysis

**Clinical Information:** The composition of urinary stones may vary from a simple crystal to a complex mixture containing several different species of crystals. The composition of the nidus (center) may be entirely different from that of the peripheral layers. Eighty percent of patients with kidney stones have a history of recurrent stone formation. Knowledge of stone composition can be useful to guide therapy of patients with recurrent stone formation. Treatment of urinary calculi is complex. In an overly simplified format, the following patterns are often treated as follows:

- **Hyperuricuria and predominately uric acid stones:** Alkalinize urine to increase uric acid solubility.
- **Hypercalciuria and predominately hydroxyapatite stones:** Acidify urine to increase calcium solubility.
- **Hyperoxaluria and calcium oxalate stones:** Increase daily fluid intake and consider reduction of daily calcium. However, treatment also depends on urine pH and urine phosphate, sulfate, oxalate, and citrate concentrations.
- **Hyperoxaluria and calcium oxalate stones:** Increase daily fluid intake and consider reduction of daily calcium.

**Useful For:** Managing patients with recurrent renal calculi

**Interpretation:** The interpretation of stone analysis results is complex, and beyond the scope of this text. We refer you to Chapter 25 of Smith LH: Diseases of the Kidney. Vol 1. Fourth edition. Edited by RW Schrier, CW Gottschalk. Boston, MA, Little, Brown and Company, 1987. Calcium oxalate stones:

- Production of calcium oxalate stones consisting of oxalate dihydrate indicate that the stone is newly formed and current urine constituents can be used to assess the importance of supersaturation.
- Production of calcium oxalate stones consisting of oxalate monohydrate indicate an old (>2 months since formed) stone and current urine composition may not be meaningful. Magnesium ammonium phosphate stones (struvite):
  - Production of magnesium ammonium phosphate stones (struvite) indicates that the cause of stone formation was infection. Treatment of the infection is the only way to inhibit further stone formation.
  - Ephedrine/guaifenesin stones:
    - Certain herbal and over-the-counter preparations (e.g., Mah Jung) contain high levels of ephedrine and guaifenesin. Excessive consumption of these products can lead to the formation of ephedrine/guaifenesin stones.

**Reference Values:**
The presence of a kidney stone is abnormal. A quantitative report will be provided after analysis.

**Clinical References:**
Kingella kingae, Molecular Detection, PCR, Blood

Clinical Information: Kingella kingae is a fastidious short Gram-negative bacillus that may colonize the oropharynx of young children. Colonization may occasionally lead to invasive disease via hematogenous dissemination, primarily in children younger than 4 years of age. This most commonly results in bone and joint infection; K kingae is the most frequent cause of osteomyelitis and septic arthritis in children aged 6 to 36 months. K kingae may also cause endocarditis, involving both native and prosthetic valves, in patients of any age and is considered part of the HACEK (Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species) group of organisms, known for causing culture-negative endocarditis. K kingae produces a repeat-in-toxin (RTX) toxin. Diagnosis of K kingae infection may be challenging due to the fastidious nature of the organism in culture. Evaluation of blood by PCR is a useful tool for the diagnosis of some cases of K kingae infection.

Useful For: Aiding in the diagnosis of Kingella kingae infection

Interpretation: A positive test is strongly suggestive of Kingella kingae infection. A negative test indicates the absence of detectable K kingae DNA, but does not negate the presence of the organism or recent disease and may occur due to sequence variability underlying primers and probes, or the presence of K kingae in quantities below the limit of detection of the assay.

Reference Values:
Not applicable

Clinical References:
Kit B

**KIT Asp816Val Mutation Analysis, Blood**

**Clinical Information:** Systemic mastocytosis is a hematopoietic neoplasm that can be included in the general category of chronic myeloproliferative disorders (CMPDs). These neoplasms are characterized by excessive proliferation of one or more myeloid lineages, with cells filling the bone marrow and populating other hematopoietic sites. In systemic mastocytosis, mast cell proliferation is the defining feature, although other myeloid lineages and B cells are frequently part of the neoplastic clone. Function-altering point mutations in KIT, a gene coding for a membrane receptor tyrosine kinase, have been found in myeloid lineage cells in the majority of systemic mastocytosis cases. The most common KIT mutation is an adenine to thymine base substitution (A->T) at nucleotide position 2468, which results in an aspartic acid to valine change in the protein (Asp816Val). Much less frequently, other mutations at this same location are found and occasional cases with mutations at other locations have also been reported. Mutations at the 816 codon are believed to alter the protein such that it is in a constitutively activated state. The main downstream effect of KIT activation is cell proliferation. Detection of a mutation at the 816 codon is included as one of the minor diagnostic criteria for systemic mastocytosis in the World Health Organization (WHO) classification system for hematopoietic neoplasms and is also of therapeutic relevance, as it confers resistance to imatinib, a drug commonly used to treat CMPDs. It is now clear that individual mast cell neoplasms are variable with respect to the number of cell lineages containing the mutation; some having positivity only in mast cells and others having positivity in additional myeloid and even lymphoid lineages. The mutation has not been reported in normal tissues.

**Useful For:** Diagnosing systemic mastocytosis in blood specimens

**Interpretation:** The test will be interpreted as positive or negative for KIT Asp816Val.

**Reference Values:**

An interpretive report will be provided indicating the mutation status as positive or negative.

**Clinical References:**


Kit AS

**KIT Asp816Val Mutation Analysis, Qualitative PCR**

**Clinical Information:** Systemic mastocytosis is a hematopoietic neoplasm that can be included in the general category of chronic myeloproliferative disorders (CMPDs). These neoplasms are characterized by excessive proliferation of one or more myeloid lineages, with cells filling the bone marrow and populating other hematopoietic sites. In systemic mastocytosis, mast cell proliferation is the defining feature, although other myeloid lineages and B cells are frequently part of the neoplastic clone. Function-altering point mutations in KIT, a gene coding for a membrane receptor tyrosine kinase, have been found in myeloid lineage cells in the majority of systemic mastocytosis cases. The most common KIT mutation is an adenine to thymine base substitution (A->T) at nucleotide position 2468, which results in an aspartic acid to valine change in the protein (Asp816Val). Much less frequently, other mutations at this same location are found and occasional cases with mutations at other locations have also been reported. Mutations at the 816 codon are believed to alter the protein such that it is in a constitutively activated state. The main downstream effect of KIT activation is cell proliferation.

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Detection of a mutation at the 816 codon is included as one of the minor diagnostic criteria for systemic mastocytosis in the World Health Organization (WHO) classification system for hematopoietic neoplasms and is also of therapeutic relevance, as it confers resistance to imatinib, a drug commonly used to treat CMPDs. It is now clear that individual mast cell neoplasms are variable with respect to the number of cell lineages containing the mutation; some having positivity only in mast cells and others having positivity in additional myeloid and even lymphoid lineages. The mutation has not been reported in normal tissues.

**Useful For:** Diagnosing systemic mastocytosis in extracted DNA specimens

**Interpretation:** The test will be interpreted as positive or negative for KIT Asp816Val.

**Reference Values:**
An interpretive report will be provided indicating the mutation status as positive or negative.

**Clinical References:**
KIT Exon 11, Mutation Analysis

Clinical Information: Several tumors can harbor KIT mutations, including gastrointestinal stromal tumors (GIST), mast cell disease, melanoma, seminoma, acute myeloid leukemia, myeloproliferative neoplasms, and lymphomas. The frequency and type of mutations vary among these tumors and portent distinct clinical implications. The ordering physician is responsible for the diagnosis and management of disease and decisions based on the data provided.

Useful For: Diagnosis and management of patients with gastrointestinal stromal tumors or melanomas Identification of a mutation in exon 11 of the KIT gene

Interpretation: Results are reported as positive, negative, or failed. A negative result does not rule out the presence of a mutation.

Reference Values:
An interpretative report will be provided.

Clinical References:

KIT Exon 13, Mutation Analysis

Clinical Information: Several tumors can harbor KIT mutations, including gastrointestinal stromal tumors (GIST), mast cell disease, melanoma, seminoma, acute myeloid leukemia, myeloproliferative neoplasms, and lymphomas. The frequency and type of mutations vary among these tumors and portent distinct clinical implications. The ordering physician is responsible for the diagnosis and management of disease and decisions based on the data provided.

Useful For: Diagnosis and management of patients with gastrointestinal stromal tumors or melanomas Identification of a mutation in exon 13 of the KIT gene

Interpretation: Results are reported as positive, negative, or failed. A negative result does not rule out the presence of a mutation.

Reference Values:
An interpretative report will be provided.

Clinical References:
KIT Exon 17, Mutation Analysis

**Clinical Information:** Several tumors can harbor KIT mutations, including gastrointestinal stromal tumors (GIST), mast cell disease, melanoma, seminoma, acute myeloid leukemia, myeloproliferative neoplasms, and lymphomas. The frequency and type of mutations vary among these tumors and portent distinct clinical implications. The ordering physician is responsible for the diagnosis and management of disease and decisions based on the data provided.

**Useful For:** Diagnosis and management of patients with gastrointestinal stromal tumors or melanomas

**Interpretation:** Results are reported as positive, negative, or failed. A negative result does not rule out the presence of a mutation.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**
KIT Exon 9, Mutation Analysis

**Clinical Information:** Several tumors can harbor KIT mutations, including gastrointestinal stromal tumors, mast cell disease, melanoma, seminoma, acute myeloid leukemia, myeloproliferative neoplasms, and lymphomas. The frequency and type of mutations vary among these tumors and portent distinct clinical implications. The ordering physician is responsible for the diagnosis and management of disease and decisions based on the data provided.

**Useful For:** Diagnosis and management of patients with gastrointestinal stromal tumors or other related tumors Identification of a mutation in exon 9 of the KIT gene

**Interpretation:** Results are reported as positive, negative, or failed. A negative result does not rule out the presence of a mutation.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

KIT Immunostain, Technical Component Only

**Clinical Information:** KIT (CD117) membrane protein is a type III tyrosine kinase growth factor receptor for stem cell factor (SCF), also known as mast cell growth factor. It is expressed in mast cells, melanocytes, and interstitial cells of Cajal. KIT is expressed in various epithelia (breast, sweat glands and salivary glands, renal tubular cells, thyroid follicular cells), testicular and ovarian interstitial cells, neurons of the central nervous system, immature myeloid cells, and trophoblastic cells. KIT staining is useful in the diagnosis of gastrointestinal stromal tumors (GISTs), germ cell tumors, mast cell disorders and acute myeloid leukemias.

**Useful For:** Aids in the identification of gastrointestinal stromal tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with
the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


KIT Mutation Exons 8-11 and 17, Hematologic Neoplasms, Sequencing, Varies

Clinical Information: Acquired mutations in the KIT gene are identified in a subset of acute myeloid leukemias (AML) characterized by inv16 or (16;16) CBFB-MYH11 or (8;21) RUNX1-RUNX1T1 genetic abnormalities (approximately 10%-20% of cases) and in this setting, the additional presence of KIT gene mutation has been described as an adverse prognostic factor in some studies. KIT mutations in AML tend to involve exons 8 through 11 and 17, although the p.Asp816Val (D816V) variant that is highly prevalent in systemic mastocytosis is less common in AML. Mastocytosis is a hematologic disorder characterized by abnormal mast cell expansion in the bone marrow and extramedullary organ sites (eg, skin, gastrointestinal tract). Disease can be localized to skin (ie, cutaneous mastocytosis) or present systemically, with variable features of disease aggressiveness and symptomatology. Mutations in the KIT gene are identified in a large majority of patients with both cutaneous mastocytosis (CM) and systemic mastocytosis (SM). The D816V abnormality is identified in most patients with SM and this finding represents an important minor diagnostic criterion in the 2008 WHO classification. The D816V is less commonly seen in CM, although single nucleotide variants are present in other KIT exons. Rare cases of familial mastocytosis are also described with KIT mutations involving exons 8 and 9. Although KIT gene mutation represents an important diagnostic marker for SM, the number of bone marrow mast cells is often limited in aspirate samples. Therefore, if SM is clinically and pathologically suspected, KIT testing should first proceed with a sensitive and specific screen for the D816V (KITB / KIT Asp816Val Mutation Analysis, Blood; KITBM / KIT Asp816Val Mutation Analysis, Qualitative PCR, Bone Marrow; or KITAS / KIT Asp816Val Mutation Analysis, Qualitative PCR) prior to consideration of KIT gene sequencing, based on the greatly enhanced sensitivity of the PCR test for this particular variant. In AML, KIT sequencing is preferred, given the wider spectrum of mutations in other KIT exons.

Useful For: Prognostic assessment of acute myeloid leukemias with core-binding factor translocations (inv16 or t[16;16] CBFB-MYH11 or t[8;21] RUNX1-RUNX1T1) Aids in establishing the diagnosis in some cases of mastocytosis

Interpretation: Mutations detected or not detected. An interpretive report will be provided.

Reference Values: An interpretive report will be provided

Kiwi Fruit, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

30% to 50% are mosaic, with either a 45,X/46,XX karyotype or a structurally abnormal X chromosome. Fewer than 15% of patients with UTS appear to have mosaicism with a 46,XY cell population or a Y chromosome rearrangement. Identifying the mosaic status of patients with UTS is of clinical importance because phenotypic expression and clinical management are dependent upon the karyotype result. Patients with a Y chromosome have a 15% to 25% increased risk of gonadoblastoma. Failure to identify an XY signal pattern does not rule out the possibility of <0.6% Y chromosome mosaicism.

**Useful For:** Detecting sex chromosome mosaicism in patients with a 45,X karyotype

**Interpretation:** An XX clone is confirmed when > or =1.0% cells display with 2 X chromosome signals. An XY clone is confirmed when > or =0.6% cells display a 1 X and 1 Y signal pattern. Females with a 45,X/46,XX karyotype have no increased risk of gonadoblastoma and generally have a more moderate expression of Turner syndrome features than females with a nonmosaic 45,X karyotype. The presence of a Y chromosome confers increased risk of gonadoblastoma.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Known Variant Analysis-1 Variant**

**Clinical Information:** This test is available for analysis of the presence of 1 sequence variant (nucleotide substitution or small insertion or deletion of nucleotides) previously identified in a family member. Targeted testing is used for diagnostic or predictive testing in cases in which variants have been previously identified in an affected family member. This testing is also used for segregation analysis to determine whether a particular variant or variants are segregating with the phenotype in an affected family. This test is used for a specific subset of genes only. Genes Available for Testing ABCC9 CFD GD1L MAGT1 PRKCD STAT3 ABCG5 CFH HAX1 MAL1 PRKDC STAT3 ABCG8 CFHR1 HRAS MAP2K1 PRKAG2 ACTA2 CFHR3 ICSOS MAP2K2 PRKG1 STK4 ACTC1 CHFR5 IGUM MEFV PSMB8 TAC1 (TNFRSF13B) ACTN2 CFI IGLL1 (Large delta) MFA5 PSTPIP1 (CD2BP1) TAP1 ACVR1L (ALK1) CHD7 IKBKB MPO PTPN11 TAP2 ADA (ADA1) CIITA IKBKG (NEMO) MS4A1 (CD20) PTPRC (CD45) TAPBP ADA2 (CECR1) COL5A1 IKZF1 (IKAROS) MTHFD1 RAC2 TAZ ADAMTS13 COL5A2 IL10 MVK RAF1 TBX1 AICDA CORO1A IL10RA MYBPC3 RAG1 TAPI CR2 (CD21) IL10RB MYH11 RAG2 TCF3 (E47) AKAP9 CRYAB IL1RN MYH6 RASA1 TERCK ANKH2 CSF2RA IL21 MYH7 RASA1 TERCK ANKH2 CSF2RA IL21 MYH7 RASA1 TERCK ANKH2 CSF2RA IL21 MYH7 RASA1 TERCK ANKH2 CSF2RA IL21 MYM2 RBCK1 (HOIL1) TGF2B AP3B1 (HP2) CSRP3 IL2RA (CD25) MYL3 RBM8A TGFBR1 ATM CTPS1 IL3RN MYLK2 RFX5 TGFBR2 BLNK CTSC IL7R MYOZ2 RFXANK THBD BRF CXCR4 ISG15 MYIN FNXAP TINF2 BTK CYBA ITCH NCB2 RH0 Roh TMEM43 C3 CYBB NCF4 RMRP TNFRSF1A CACNA1C DCLRE1C (ARTEMIS) ITK NEXN RNFL168 C5A13 CACNA2D1 DES JAK3 NFKB2 RTEL1 TNFRSF4 (OX40) CACNB2 DGKE JUP NFKB1A (IKBA) RYR2 TNFSF12 (TWEAK) CARD11 DKC1 KNC1 NEJ11 SBDS TNN1 CARD14 DPYD KCNE2 NPHP SC1B1 TNN15 CAV3 DSC2 KCNE1 LRP3 SCN3B TNNT2 CB1 DSG2 KCNH2 NLRP3 (C1AS1) SCN4B TPM1 CBS DSP KNC15 NOD2 (CARD15) SCN5A TRAC CD19 DTNA KNC18 NOD10 SEMA3E TTC37 CD247 (CD32) ELANE (ELA2) KNC15 NOTCH1 SGCD MHC7B ENG KRS NRS H2D1A TTN CD3D FBN1 LAMA4 ORAI1 SH3BP2 TTR CD3E FBN2 LAMP2 PCSK9 SHOC2 UNG CD3G FERMT3 LAMTOR2 (MAPBBP) PIK3R1 SKI USP1 (C16ORF57) CD40 FLNA LCK PIK3CD SLCA210 VCL CD40LG FOXL1 LDB3 PKLR SLCA314 VPS13B (COH1) CD46 (MCP) FOXP3 DLK1 PRK2 LSC46A1 VPS45 CD79A FPR1 LDLRA1 PLGC2 SMAD3 WAS CD79B (B29) G6PC3 LIG4 PLG SMAD4 WIPF1 CD8A GATA2 LMNA PLN STRATT1 WRAP53 CD81 GDF2 (BMP9) LPIN2 PPM2 (CD2G) SOSI XIAP (BIRC4) CEBPE FII LRBA PNP SPINK5 ZAP70 CFB GLA LRR5A Refer to the following resources for information regarding the listed gene targets. GeneReviews-NCBI Bookshelf, available at www.ncbi.nlm.nih.gov/books/NBK1116/ or OMIM, available at www.omim.org/ If testing is needed for a
Useful For: Diagnostic or predictive testing for specific conditions when a DNA sequence variant of interest has been previously identified in a family member, and follow-up testing for this specific variant in other family members is desired. Carrier screening for individuals at risk for having a DNA sequence variant that was previously identified in a family member. Segregation analysis for a single familial DNA sequence variant.

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics recommendations as a guideline.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


KVAR2

Known Variant Analysis-2 Variants

Clinical Information: This test is available for analysis of the presence of 2 sequence variants (nucleotide substitution or small insertion or deletion of nucleotides) previously identified in a family member. Targeted testing is used for diagnostic or predictive testing in cases in which variants have been previously identified in an affected family member. This testing is also used for segregation analysis to determine whether a particular variant or variants are segregating with the phenotype in an affected family. This test is used for a specific subset of genes only. Genes Available for Testing: ABCC9, CFD, GPD1L, MAGT1, PRKCD, STAT3, ABCG5, CFH, HAX1, MALT1, PRKDC, STAT5B, ABCG8, CFHR1, HRAS, MAP2K1, PRKAG2, STIM1, ACTA2, CFHR3, ICOS, MAP2K2, PRKG1, STK4, ACTC1, CFHR5, IGTH, MEFV, PSMB8, TACI (TNFRSF13B), ACTN2, CFH, RAG1, WAS.

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 1325
Mutation, Targeted Testing, which includes targeted/site-specific testing for additional genes. Testing may be delayed if required documentation (ie, patient information sheet) is not received.

**Useful For:** Diagnostic or predictive testing for specific conditions when 2 DNA sequence variants of interest have been previously identified in a family member, and follow-up testing for these specific variants in other family members is desired. Carrier screening for individuals at risk for having 2 DNA sequence variants that were previously identified in a family member. Segregation analysis for 2 familial DNA sequence variants.

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.


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**Known Variant Analysis-3+ Variants**

**Clinical Information:** This test is for analysis of the presence of 3 to 5 sequence variants (nucleotide substitution or small insertion or deletion of nucleotides) previously identified in a family member. Targeted testing is used for diagnostic or predictive testing in cases in which variants have been previously identified in an affected family member. This testing is also used for segregation analysis to determine whether a particular variant or variants are segregating with the phenotype in an affected family. This test is used for a specific subset of genes only. Genes Available for Testing ABCC9 CFD GPD1L MAGT1 PRKCD STAT3 ABCG5 CFH HAX1 MALTI1 PRKDC STAT5B ABCG8 CFHR1 HRS MAP2K1 PRKAG2 STIM1 ACTA2 CFHR3 ICOS MAP2K2 PRK1 STK4 ACT1 CFHR5 IGME MFVE PSMB8 CFRC13 (TNRFSF13B) ACTN2 CFI IGL1 (Lambda5) MFAP5 PSTPIP1 (CD2BP1) TAP1 ACVR1L1 (ALK1) CHD7 IKBKB MPO PTPN11 TAP2 ADA (ADA1) CIITA IKBKGNEMO MS4A1 (CD20) PTPRC (CD45) TAPBP ADA2 (CECR1) COL5A1 IZKF1 (IKAROS) MTHFD1 RAC2 TAZ ADAMTS1 COL5A2 IL10 MVK RAF1 TBX1 AICDA CORO1A IL10RA MYBPC3 RAG1 TAP AK2 CR2 (CD21) IL10RB MYH11 RAG2 TCF3 (E47) AKAP9 CRYAB IL1RN MYH6 RASA1 TERC ANK2 CSF2RA IL21 MYH7 FASGRP2 TERT ANKRD1 CSF3R IL2R MYL2 RBCK1 (HOIL1) TGFBR2 AP3B1 (HP2) CSRP3 IL2RA (CD25) MYL3 RBMA8 TGFBR1 ATM CTPS1 IL36RN MYLK2 RFX5 CTSC IL7R MYOZ2 RXANK THBD BRAF CXCR4 ISG15 MYPN RFXAP TINF2 BTK CYBA ITCH NCF2 RH0H TEMEM3 C3 CYBB ITGB2 NCF4 RMRP TNFRSF1A CACNA1C DCLRE1C (ARTEMIS) ITK NEXN RNF168 TNRFSF13C CACNA2D1 DES JAK3 NFKB2 RTEL1 TNFRSF4 (OX40) CACNB2 DGKE JUP NFKBIA (IKBa) RYR2 TNFRSF12 (TWEAK) CARD11 DC1 KIC1 KCE1 NHE1 JBD1 TNCN1 CARD14 DPYD KCNE2 NHP2 SCN1B TNI13 CAV3 DSC2 KCNE3 NLRP12 SCN3B TNNT2 CBL DSG2 KCNH1 NLRP3 (C1AS1) SCN4B TPM1 CBS DSP KCNJ5 NOD2 (CARD15) SCN5A TRAC CD19 DTNA KCNJ8 NOP10 SEMA3E TCC3 CD247 (CD3Z) ELANE (ELA2) KCNQ1 NOTCH1 SGCD TCT7A CD27 ENG KRAS NARAS SH2D1A TTN CD3D FB1 LAMA4 ORAI1 SH3BP2 TTR CD3E FBN2 LAMPAK SHOC2 UNCD3G FERM1 LAMTOR2 (MAPB2P) PIK3K1 SKI USBI (C16ORF57) CD40 FLNA LCK PIK3CD SLCA2A10 VCL CD40LG FOXN1 LDB3 PLKR SLC37A4 VPS13B (COH1) CD46 (MCP) FOXO3 LDRK PKP2 SLC46A1 CD79A FRP1 LDRR1 PKL GL2 SMAD3 WAS CD79B (B29) G6PC3 LG4 PLG SMAD4 WIPF1 CD8A GATA2 LMNA PLN SNTA1 WRAP53 CD81 GDF2 (BMP9) LPIN2 PMM2 (CDG1) SOS1 XIAP (BIRC4) CEBPE GF11 LRBA PNP SPINK5 ZAP70 CFB GLA LRRCA8. Refer to the following resources for information regarding the listed gene targets. GeneReviews-NCBI Bookshelf, available at www.ncbi.nlm.nih.gov/books/NBK1116/ or OMIM, available at www.omim.org/. If testing is needed for a gene not on this list, see FMTT / Familial Mutation, Targeted Testing, which includes targeted/site-specific testing for additional genes.
Useful For: Diagnostic or predictive testing for specific conditions when 3 to 5 DNA sequence variants of interest have been previously identified in a family member, and follow-up testing for these specific variants in other family members is desired. Carrier screening for individuals at risk for having 3 to 5 DNA sequence variants that were previously identified in a family member. Segregation analysis for 3 to 5 familial DNA sequence variants.

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.


KPC (blaKPC) and NDM (blaNDM) in Gram-Negative Bacilli, Molecular Detection, PCR

Clinical Information: Nonsusceptibility to carbapenems in gram-negative bacilli by means of the enzyme KPC (Klebsiella pneumoniae carbapenemase) or NDM (New Dehli metallo-beta-lactamase) is becoming more common. The genes blaKPC and blaNDM encode KPC and NDM enzyme production, respectively. In addition to KPC and NDM production, there are other mechanisms of resistance to carbapenems in gram-negative bacilli, including production of other carbapenemases, or plasmid-encoded AmpC, or extended beta-lactamase production combined with decreased membrane permeability. Detection of carbapenemases by the modified Hodge test may be subjective and is not rapid. Testing for the minimum inhibitory concentration (MIC) determines the level but not the mechanism of resistance. PCR is a sensitive, specific, and rapid means of detecting of a specific portion of the genes encoding KPC and NDM production.

Useful For: Assessing pure isolates of gram-negative bacilli for mechanism of carbapenem resistance

Interpretation: This PCR detects and differentiates both blaKPC and blaNDM. A positive KPC (Klebsiella pneumoniae carbapenemase) PCR indicates that the isolate carries blaKPC. A positive NDM (New Dehli metallo-beta-lactamase) PCR indicates the isolate carries blaNDM. A negative result indicates the absence of detectable blaKPC or blaNDM DNA; however, false-negative results may occur due to inhibition of PCR, sequence variability underlying primers and, or loss of a plasmid carrying blaKPC and blaNDM.

Reference Values:
Not applicable

surveillance to detect unrecognized colonized patients who may be a potential source for carbapenem-resistant (drug-resistant) Enterobacteriaceae (CRE) transmission. Such surveillance testing may be focused in certain high-risk settings or patient groups (eg, ICUs, long-term acute care, patients transferred from areas or facilities with high CRE prevalence) or by infection control to investigate an outbreak. Nonsusceptibility to carbapenems in gram-negative bacilli by means of the enzyme KPC (Klebsiella pneumoniae carbapenemase) or NDM (New Delhi metallo-beta-lactamase) is becoming more common. The genes blaKPC and blaNDM encode KPC and NDM enzyme production, respectively. PCR is a sensitive, specific, and rapid means identifying patients colonized by CRE harboring blaKPC or blaNDM.

**Useful For:** Identifying carriers of carbapenem-resistant Enterobactericeae harboring KPC (Klebsiella pneumoniae carbapenemase) or NDM (New Delhi metallo-beta-lactamase) genes

**Interpretation:** This PCR detects and differentiates blaKPC and blaNDM in surveillance specimens (perirectal/rectal swabs or stool). A positive KPC (Klebsiella pneumoniae carbapenemase) and/or NDM (New Delhi metallo-beta-lactamase) PCR indicates that the patient is colonized by a Gram-negative bacillus (or Gram-negative bacilli) harboring a carbapenemase gene, blaKPC and/or blaNDM, respectively. A negative result indicates the absence of detectable DNA; however, false-negative results may occur due to inhibition of PCR, sequence variability underlying primers and probes, or the presence of the blaKPC or blaNDM genes in quantities less than the limit of detection of the assay.

**Reference Values:**
Not applicable

**Clinical References:**

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**KPND1**
**KPC and NDM PCR (Bill Only)**

**Reference Values:**
This test is for Billing Purposes Only.
This is not an orderable test.

**KD2T**
**Krabbe Disease Second-Tier Newborn Screen, Blood Spot**

**Clinical Information:** Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by a deficiency of galactocerebrosidase leading to an accumulation of galactosylsphingosine and severe demyelination throughout the brain. Krabbe disease is primarily caused by mutations in the GALC gene, and it has an estimated frequency of 1 in 100,000 births. The clinical course of Krabbe disease can be variable, even within the same family. Eighty-five percent to 90% of patients present before the first year of life with central nervous system impairment including increasing irritability, developmental delay, and sensitivity to stimuli. Rapid neurodegeneration including white matter disease is followed by death usually by age 2. Ten percent to 15% of individuals have late onset forms of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression presenting anytime from age 6 months to the seventh decade of life. Newborn screening for Krabbe disease has recently been implemented in some states. The early (presymptomatic) identification and subsequent testing of infants at risk for Krabbe disease may be helpful in reducing the morbidity and mortality associated with this disease. While treatment is mostly supportive, hematopoietic stem cell transplantation has shown some
success if performed prior to onset of neurologic damage. Newborn screening can typically identify patients with Krabbe disease, even before onset of symptoms and also unaffected patients with GALC pseudodeficiency alleles. For these reasons, second-tier testing that includes both psychosine and 30-kb deletion analyses has been developed. Second-tier testing reduces the number of false-positive results and also limits the identification of affected individuals to patients needing immediate follow-up. Psychosine (PSY), a neurotoxin at elevated concentrations, is 1 of 4 substrates degraded by galactocerebrosidase. It has been shown to be elevated in patients with active disease and, therefore, may be a useful biomarker for the presence of disease or disease progression. The common 30-kb deletion spanning intron 10 through the end of the gene accounts for a significant proportion of disease alleles that contribute to infantile Krabbe disease. While enzyme activity alone is not predictive of age of onset, there are known genotype-phenotype correlations. Individuals who are homozygous for the deletion or compound heterozygous for the deletion and a second GALC mutation (with the exception of late-onset mutations) are predicted to have infantile Krabbe disease. Although rare, a few infants with an early onset Krabbe disease phenotype due to deficiency of saposin A (SAP-A) have been found. Saposin-A is a sphingolipid activator protein that assists galactocerebrosidase in its action on galactosylceramide.

**Useful For:** Second-tier testing of newborns with an abnormal screening result for Krabbe disease
Follow-up testing after an abnormal newborn screening result for Krabbe disease

**Interpretation:** An interpretive report is provided. An elevation of psychosine is indicative of symptomatic Krabbe disease. The presence of a homozygous 30-kb deletion is indicative of early onset Krabbe disease.

**Reference Values:** An interpretive report is provided.

**Clinical References:**
mutations in the GALC gene that are identifiable by molecular genetic testing. The above tests are not reliable for detection of carriers of Krabbe disease. Molecular genetic testing (this test) is the recommended test for individuals with a family history of Krabbe disease in which the mutations in the family are unknown. Molecular tests form the basis of confirmatory or carrier testing. This assay includes DNA sequencing of all 17 exons within the GALC gene as well as evaluation for the common 30-kb deletion spanning intron 10 through the end of the gene. This deletion accounts for a significant proportion of disease alleles that contribute to infantile Krabbe disease. While enzyme activity is not predictive of age of onset, there are known genotype-phenotype correlations. Individuals who are homozygous for the deletion or compound heterozygous for the deletion and a second GALC mutation (with the exception of late-onset mutations) are predicted to have infantile Krabbe disease. The c.857G->A (p.Gly286Asp) mutation, on the other hand, is only associated with a late-onset phenotype.

**Useful For:** Second-tier test for confirming a diagnosis of Krabbe disease Carrier testing for individuals with a family history of Krabbe disease in the absence of known mutations in the family

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**KRAS Mutation Analysis, 7 Mutation Panel, Colorectal**

**Clinical Information:** Colorectal cancer is currently among the most common malignancies diagnosed each year. Strategies that focus on early detection and prevention effectively decrease the risk of mortality associated with the disease. In addition, an increase in survival rate for individuals with advanced stage colorectal cancer has been observed as a result of advancements in standard chemotherapeutic agents and the development of specialized targeted therapies. Monoclonal antibodies against epidermal growth factor receptor (EGFR), such as cetuximab and panitumumab, represent a new area of targeted therapy for such patients. However, studies have shown that not all individuals with colorectal cancer respond to EGFR-targeted molecules. Because the combination of targeted therapy and standard chemotherapy leads to an increase in toxicity and cost, strategies that help to identify the individuals most likely to benefit from such targeted therapies are desirable. EGFR is a growth factor receptor that is activated by the binding of specific ligands (epiregulin and amphiregulin), resulting in activation of the RAS/MAPK pathway. Activation of this pathway induces a signaling cascade ultimately regulating a number of cellular processes including cell proliferation. Dysregulation of the RAS/MAPK pathway is a key factor in tumor progression. Targeted therapies directed to EGFR, which inhibit activation of the RAS/MAPK pathway, have demonstrated some success (increased progression-free and overall survival) in patients with colorectal cancer. One of the most common somatic alterations in colon cancer is the presence of activating mutations in the proto-oncogene KRAS. KRAS is recruited by ligand-bound (active) EGFR to initiate the signaling cascade induced by the RAS/MAPK pathway. Because mutant KRAS constitutively activates the RAS/MAPK pathway downstream of EGFR, agents such as cetuximab and panitumumab, which prevent ligand-binding to EGFR, do not appear to have any meaningful inhibitor activity on cell proliferation in the presence of mutant KRAS. Current data suggest that the efficacy of EGFR-targeted therapies in colon cancer is confined to patients with tumors lacking KRAS mutations. As a result, the mutation status of KRAS can be a useful marker by which patients are...
selected for EGFR-targeted therapy. At this time, this test is approved specifically for colorectal tumors and metastatic lesions from a colorectal primary. Please refer to KRASO / KRAS Mutation Analysis, 7 Mutation Panel, Other (Non-Colorectal) for KRAS testing in noncolorectal tumors.

**Useful For:** Prognostic markers for cancer patients treated with epidermal growth factor receptor-targeted therapies

**Interpretation:** An interpretative report will be provided.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

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**KRASO**

**KRAS Mutation Analysis, 7 Mutation Panel, Other (Non-Colorectal)**

**Clinical Information:** Lung cancer is the leading cause of cancer-related deaths in the world. Non-small cell lung cancer (NSCLC) represents 70% to 85% of all lung cancer diagnoses. Randomized trials have suggested that targeted agents alone or combined with chemotherapy may be beneficial. Because the addition of targeted therapy may lead to an increase in toxicity and cost, strategies that help to identify the individuals most likely to benefit from targeted therapies are desirable. Monoclonal antibodies against epidermal growth factor receptor (EGFR) represent a new area of targeted therapy for such patients. However, studies have shown that not all individuals with NSCLC respond to these EGFR-targeted molecules. EGFR is a growth factor receptor that is activated by the binding of specific ligands (epiregulin and amphiregulin), resulting in activation of the RAS/MAPK pathway. Activation of this pathway induces a signaling cascade ultimately leading to cell proliferation. Dysregulation of the RAS/MAPK pathway is a key factor in tumor progression. Targeted therapies directed to EGFR, which inhibit activation of the RAS/MAPK pathway, have demonstrated some success in treating a subset of patients with NSCLC. In NSCLC, one of the most frequently reported alterations in the EGFR-signaling pathway is the presence of a mutation in the proto-oncogene KRAS. KRAS is recruited by ligand-bound (active) EGFR to initiate the signaling cascade induced by the RAS/MAPK pathway. Because mutant KRAS constitutively activates the RAS/MAPK pathway downstream of EGFR, agents that prevent ligand-binding to EGFR do not appear to have any meaningful inhibitor activity on cell proliferation in the presence of mutant KRAS. Current data suggest that the efficacy of EGFR-targeted therapies in NSCLC is confined to patients with tumors lacking KRAS mutations. As a result, the mutation status of KRAS can be a useful marker by which patients are selected for EGFR-targeted therapy. At this time, this test is for unknown and/or unidentified primary tumors, primary tumors other than colorectal, and metastatic lesions from a primary other than colorectal. Please refer to KRASC / KRAS Mutation Analysis, 7 Mutation Panel, Colorectal for KRAS testing in colorectal tumors.

**Useful For:** Prognostic marker for cancer patients with noncolorectal tumors treated with epidermal growth factor receptor-targeted therapies

**Interpretation:** An interpretative report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
2. Ladanyi M, Pao W: Lung adenocarcinoma: guiding EGFR-targeted
Lacosamide, Serum

Clinical Information: Lacosamide is approved for adjunctive therapy to treat partial-onset seizures in epileptic patients 17 years of age and older. In clinical trials, the most common side effects were dizziness, headache, nausea, and double vision. Lacosamide is completely absorbed after oral administration with negligible first-pass metabolism. Peak plasma concentrations occur 1 to 4 hours after oral dosing, and the elimination half-life is approximately 13 hours. Steady-state plasma concentrations are achieved after 3 days of twice daily repeated administration. About 40% of the administered dose is eliminated by the renal system unchanged and 30% is metabolized by hepatic isoenzymes (CYP2C9, CYP2C19, and CYP3A4) to the O-desmethyl inactive metabolite. The relationship between lacosamide plasma concentrations and its efficacy or adverse effects is not well established. However, central nervous system toxicity has been associated with higher drug concentrations in plasma.

Useful For: Monitoring serum concentrations of lacosamide to ensure compliance and appropriate dosing in specific clinical conditions (ie, severe renal impairment, mild-to-moderate hepatic impairment, and end-stage renal disease)

Interpretation: The serum concentration should be interpreted in the context of the patient's clinical response and may provide useful information in patients showing poor response or adverse effects, particularly when lacosamide is coadministered with other anticonvulsant drugs. Toxic ranges have not been established.

Reference Values:
Patients receiving therapeutic doses usually have lacosamide concentrations of 1.0-10.0 mcg/mL.

Clinical References:

Lactate Dehydrogenase (LD) Isoenzymes, Serum

Clinical Information: Total Lactate Dehydrogenase (LD): LD activity is present in all cells of the body with highest concentrations in heart, liver, muscle, kidney, lung, and erythrocytes. As with other proteins used as tissue-function markers, the appearance of LD in the serum occurs only after prolonged hypoxia and is elevated in a number of clinical conditions including cardiorespiratory diseases, malignancy, hemolysis, and disorders of the liver, kidneys, lung, and muscle. Isoenzymes: LD is a tetrameric cytoplasmic enzyme, composed of H and M subunits. The usual designation of the isoenzyme is LD-I (H4), LD-II (H3M), LD-III (H2M2), LD-IV (HM3), and LD-V (M4). Tissue specificity is derived from the fact that tissue-specific synthesis of subunits occurs in well-defined ratios. Most notably, heart muscle cells preferentially synthesize H subunits, while liver cells synthesize M subunits nearly exclusively. Skeletal muscle also synthesizes largely M subunits so that LD-V is both a liver and skeletal muscle form of LD. The LD-I and LD-V forms are most often used to indicate heart or liver pathology, respectively. LD-I appears elevated in the serum about 24 to 48 hours after a myocardial infarction (MI), but is generally not as useful as troponin for detection of MI, unless the MI occurred at least 24 hours prior to testing. Normally, LD-II is greater than LD-I; however, when a MI has occurred, there is a "flip" in the usual ratio of LD-I/LD-II from less than 1 to greater than 1 (or at least >0.9). Use of the ratio for
evaluation of patients with possible cardiovascular injury has largely been replaced by TPNT / Troponin T, Serum. The LD-V form is pronounced in patients with either primary liver disease or liver hypoxia secondary to decreased perfusion, such as occurs following an MI. However, LD-V is usually not as reliable as the transaminases (eg, aspartate aminotransferase, alanine aminotransferase) for evaluating liver function. LD-V also may be elevated in muscular damage and diseases of the skin. Although it does not appear to cause or be associated with any symptoms or particular diseases, the presence of macro-LD (LD combined with an immunoglobulin) can cause an idiosyncratic elevation of total LD.

Useful For: Investigating a variety of diseases involving the heart, liver, muscle, kidney, lung, and blood Differentiating heart-synthesized lactate dehydrogenase (LD) from liver and other sources Investigating unexplained causes of LD elevations Detection of macro-LD

Interpretation: Marked elevations in lactate dehydrogenase (LD) activity can be observed in megaloblastic anemia, untreated pernicious anemia, Hodgkin disease, abdominal and lung cancers, severe shock, and hypoxia. Moderate-to-slight increases in LD levels are seen in myocardial infarction (MI), pulmonary infarction, pulmonary embolism, leukemia, hemolytic anemia, infectious mononucleosis, progressive muscular dystrophy (especially in the early and middle stages of the disease), liver disease, and renal disease. In liver disease, elevations of LD are not as great as the increases in aspartate amino transferase and alanineaminotransferase. Increased levels of the enzyme are found in about one-third of patients with renal disease, especially those with tubular necrosis or pyelonephritis. However, these elevations do not correlate well with proteinuria or other parameters of renal disease. On occasion, a raised LD level may be the only evidence to suggest the presence of a hidden pulmonary embolus. Isoenzymes: LD-II is found in myocardium. Following a severe MI, the diagnostic ratio of LD-I divided by LD-II will change from less than 0.9 to greater than 0.9. This is referred to as an LD "flip". LD-I elevation not due to myocardial damage may indicate hemolytic disease or other forms of in vivo hemolysis. Elevation of LD-V (least mobile isoenzyme) usually denotes liver damage. It is rarely helpful in defining skeletal muscle disease. Macro-LD can occur, which results in an elevation of LD for no clinical reason. Macro-LD greatly affects the migration of LD isoenzymes since the addition of an immunoglobulin molecule greatly retards the migration of the usual LD isoenzymes. If macro-LD is present, the electrophoretogram will show atypically migrating isoenzymes with LD activity localized near the origin.

Reference Values:

**LACTATE DEHYDROGENASE (LD)**

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<td>135-750 U/L</td>
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<td>31 days-11 months</td>
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**LD ISOENZYMES**

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<td>IV</td>
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<tr>
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</tbody>
</table>

Measurement of LD in body fluids is primarily indicated to aid in the differentiation of transudative and exudative effusions as LD activity is considered an indicator of the extent of inflammation. Dr. Richard Light derived criteria in the 1970s for patients with pleural effusions that are still used today. The criteria include the measurement of total protein and LD in pleural fluid and serum. Exudates are defined as meeting 1 of the following criteria: 1. Pleural fluid-to-serum protein ratio above 0.5 2. Pleural fluid LD above two-thirds the upper limit of normal serum LD 3. Pleural fluid-to-serum LD ratio above 0.6 Pericardial fluid: The routine analysis of LD to differentiate exudative and transudative pericardial effusions is not considered helpful. Peritoneal fluid: Ascitic fluid LD has reported utility in differentiating secondary bacterial peritonitis from spontaneous bacterial peritonitis when at least 2 of 3 criteria are met in ascites fluid: total protein above 1.0 g/dL, glucose below 50 mg/dL, and LD above the upper reference limit for serum. Spinal fluid (CSF): LD is not measured in CSF routinely. Release of LD into CSF occurs as a consequence of cell death. Therefore, LD is a nonspecific marker of cell necrosis and may be raised in a number of pathologic conditions, including meningitis with normal concentrations reported as less than 24 U/L. CSF LDH is also increased in primary brain tumors, central nervous system metastases, hydrocephalus, and cerebral ischemia.

Useful For: Identification of exudative pleural effusions

Interpretation: Elevated lactate dehydrogenase in pleural fluid is consistent with exudative effusions.


Lactate Dehydrogenase (LD), Serum

Clinical Information: Lactate dehydrogenase (LD) activity is present in all cells of the body with highest concentrations in heart, liver, muscle, kidney, lung, and erythrocytes. Serum LD is elevated in a number of clinical conditions.

Useful For: Investigation of a variety of diseases involving the heart, liver, muscle, kidney, lung, and blood Monitoring changes in tumor burden after chemotherapy, although, lactate dehydrogenase elevations in patients with cancer are too erratic to be of use in the diagnosis of cancer

Interpretation: Marked elevations in lactate dehydrogenase (LD) activity can be observed in megaloblastic anemia, untreated pernicious anemia, Hodgkin disease, abdominal and lung cancers, severe shock, and hypoxia. Moderate to slight increases in LD levels are seen in myocardial infarction (MI), pulmonary infarction, pulmonary embolism, leukemia, hemolytic anemia, infectious mononucleosis, progressive muscular dystrophy (especially in the early and middle stages of the disease), liver disease, and renal disease. In liver disease, elevations of LD are not as great as the increases in aspartate amino transferase (AST) and alanine aminotransferase (ALT). Increased levels of the enzyme are found in about one-third of patients with renal disease, especially those with tubular necrosis or pyelonephritis. However, these elevations do not correlate well with proteinuria or other parameters of renal disease. On occasion a raised LD level may be the only evidence to suggest the presence of a hidden pulmonary embolus.

Reference Values:
1-30 days: 135-750 U/L
31 days-11 months: 180-435 U/L
1-3 years: 160-370 U/L
4-6 years: 145-345 U/L
7-9 years: 143-290 U/L
10-12 years: 120-293 U/L
13-15 years: 110-283 U/L

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
16-17 years: 105-233 U/L
> or =18 years: 122-222 U/L


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**LABF 8030**

**Lactate, Body Fluid**

**Clinical Information:** Lactate found in cerebrospinal fluid (CSF) is predominantly produced by central nervous system (CNS) glycolysis and is independent of serum lactate. Increased CSF lactate concentrations are related to increased cerebral glycolysis or hypoxia associated with bacterial meningitis, cerebral infarction, cerebral arteriosclerosis, intracranial hemorrhage, hydrocephalus, traumatic brain injury, cerebral edema, epilepsy, and inborn errors of metabolism. Lactate measurement in CSF has been proposed as a test to differentiate bacterial from viral meningitis.

**Useful For:** Aid in differentiating between bacterial and viral meningitis Aid in identifying increased glycolysis or hypoxia associated with bacterial meningitis, cerebral infarction, cerebral arteriosclerosis, intracranial hemorrhage, hydrocephalus, traumatic brain injury, cerebral edema, epilepsy, and inborn errors of metabolism

**Interpretation:** Published studies suggest normal cerebrospinal fluid (CSF) lactate concentration is 1.1 to 2.3 mmol/L and meta-analysis of 33 studies concluded concentrations >3.9 mmol/L are suggestive of bacterial meningitis, with lower concentrations suggestive of viral meningitis.

**Reference Values:**
Not applicable


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**LAA 8665**

**Lactate, Plasma**

**Clinical Information:** Lactate is the end product of anaerobic carbohydrate metabolism. Major sites of production are skeletal muscle, brain, and erythrocytes. Lactate is metabolized by the liver. The concentration of lactate depends on the rate of production and the rate of liver clearance. The liver can adequately clear lactate until the concentration reaches approximately 2 mmol/L. When this level is exceeded, lactate begins to accumulate rapidly. For example, while resting lactate levels are usually <1 mmol/L, during strenuous exercise levels can rise >20 mmol/L within a few seconds. Lactic acidosis signals the deterioration of the cellular oxidative process and is associated with hyperpnea, weakness, fatigue, stupor, and finally coma. These conditions may be irreversible, even after treatment is administered. Lactate acidosis may be associated with hypoxic conditions (eg, shock, hypovolemia, heart failure, pulmonary insufficiency), metabolic disorders (eg, diabetic ketoacidosis, malignancies), and toxin exposures (eg, ethanol, methanol, salicylates).

**Useful For:** Diagnosing and monitoring patients with lactic acidosis

**Interpretation:** While no definitive concentration of lactate has been established for the diagnosis of lactic acidosis, lactate concentrations exceeding 5 mmol/L and pH <7.25 are generally considered indicative of significant lactic acidosis.

**Reference Values:**
< or =2 years: 0.6-3.2 mmol/L  
>2 years: 0.6-2.3 mmol/L

**Clinical Information:** Anaerobic glycolysis markedly increases blood lactate and causes some increase in pyruvate levels, especially with prolonged exercise. The common cause for increased blood lactate and pyruvate is anoxia resulting from such conditions as shock, pneumonia, and congestive heart failure. Lactic acidosis may also occur in renal failure and leukemia. Thiamine deficiency and diabetic ketoacidosis are associated with increased levels of lactate and pyruvate. Lactate measurements that evaluate the acid-base status are used in the diagnosis and treatment of lactic acidosis (abnormally high acidity in the blood).

**Useful For:** Diagnosing and monitoring patients with lactic acidosis

**Interpretation:** While no definitive concentration of lactate has been established for the diagnosis of lactic acidosis, lactate concentrations exceeding 5 mmol/L and pH below 7.25 are generally considered indicative of significant lactic acidosis.

**Reference Values:**
- 0-90 days (<3 months): < or =3.3 mmol/L
- 3-24 months: < or =3.1 mmol/L
- >24 months-18 years: < or =2.2 mmol/L
- >18 years: 0.5-2.2 mmol/L


**Clinical Information:** Anaerobic glycolysis markedly increases lactate concentrations. Lactate concentrations in cerebrospinal fluid (CSF) are increased in the presence of cerebral glycolysis or hypoxia associated with bacterial meningitis, cerebral infarction, cerebral arteriosclerosis, intracranial hemorrhage, hydrocephalus, traumatic brain injury, cerebral edema, epilepsy, and inborn errors of metabolism. Lactate found in CSF is predominantly produced by central nervous system (CNS) anaerobic glycolysis and is independent of blood lactate. Lactate measurement in CSF has been proposed as a test to differentiate bacterial from viral meningitis.

**Useful For:** Aid in differentiating between bacterial and viral meningitis Aid in identifying increased anaerobic glycolysis or hypoxia associated with bacterial meningitis, cerebral infarction, cerebral arteriosclerosis, intracranial hemorrhage, hydrocephalus, traumatic brain injury, cerebral edema, epilepsy, and inborn errors of metabolism

**Interpretation:** In addition to reference intervals, published meta-analysis of 33 studies concluded concentrations greater than 3.9 mmol/L are suggestive of bacterial meningitis, with lower concentrations suggestive of viral meningitis.(1)

**Reference Values:**
- 0-2 days: 1.1-6.7 mmol/L
- 3-10 days: 1.1-4.4 mmol/L
- 11 days-17 years: 1.1-2.8 mmol/L
- >17 years: 1.1-2.4 mmol/L

**Interpretation:** A positive result is indicative of the presence of lactoferrin, a marker for fecal leukocytes. A negative result does not exclude the presence of intestinal inflammation.

**Reference Values:**
Negative

**LACTO 70625**

**Lactotransferrin IHC, Technical Component Only**

**Clinical Information:** Lactotransferrin (also referred to as lactoferrin) is a secreted iron-binding glycoprotein found in milk, tears, and leukocytes. It has been shown to be expressed in various tissues including tonsil, intestinal epithelium, kidney, and various regions of the brain where it is thought to play a role in iron metabolism and defense against bacteria. Lactotransferrin also plays a role in amyloidosis, specifically of the cornea, but has been observed in other tissue types.

**Useful For:** Identifying the presence of lactotransferrin in amyloid deposits An adjunct to amyloid subtyping analysis by mass spectrometry

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**FLBAE 57572**

**Ladybeetle Multicolored Asian (Harmonia axyridis) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

**LAMQ 82682**

**Lamb's Quarter, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of
sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
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</tr>
<tr>
<td>1</td>
<td>0.35-0.69 Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49 Positive</td>
</tr>
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<tr>
<td>4</td>
<td>17.5-49.9 Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9 Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Lamb, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the
concentration of IgE antibodies expressed as a class score or kU/L.

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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>= or &gt;100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**LAIHC 70499**

**Lambda Light Chain (Lambda-C) Immunostain, Technical Component Only**

**Clinical Information:** Kappa or lambda immunoglobulin light chains pair with immunoglobulin heavy chains to form complete immunoglobulin molecules. These proteins serve as receptors for antigens in B-lymphocytes and are the secretory products of plasma cells, forming the humoral arm of the immune system. Because individual B cells or plasma cells synthesize immunoglobulin containing either kappa or lambda light chains, but not both, immunoperoxidase stains for light chains can be applied to lymphocyte and plasma cell populations as a marker of clonality and B-cell lineage.

**Useful For:** A marker of B-cell and plasma cell clonality and B-cell lineage

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**LBC 60450**

**Lamellar Body Count, Amniotic Fluid**

**Clinical Information:** Fetal lung maturity testing is used to determine the risk for developing respiratory distress syndrome (RDS) in infants born prematurely (32-39 weeks). The risk for developing RDS is inversely related to gestational age and is the most common cause of respiratory failure in
neonates. RDS is associated with preterm birth due to insufficient production of pulmonary surfactant. Pulmonary surfactant is synthesized by type II pneumocytes. Surfactant consists of 90% phospholipids (primarily phosphatidylcholine and phosphatidylglycerol) and 10% proteins (surfactant proteins [SP]-A, SP-B, SP-C). Surfactant is packaged into lamellar bodies and is excreted into the alveolar space where it unravels and forms a monolayer on alveolar surfaces. Lamellar bodies can also pass into the amniotic cavity and, hence, are found in amniotic fluid. The surfactant functions to reduce the surface tension in the alveoli, preventing atelectasis. When surfactant is deficient, the small alveoli collapse and the large alveoli become overinflated and stiff, which has been associated with increased risk of developing respiratory distress. The status of fetal lung maturity is reflected in the concentration of surfactant in the form of phospholipids and lamellar bodies present in amniotic fluid. Lamellar bodies are similar in size to platelets and can be quantified on a hematology analyzer utilizing the platelet channel and used to estimate fetal lung maturity.

**Useful For:** Predicting fetal lung maturity and assessing the risk of developing neonatal respiratory distress syndrome, when performed during 32 to 39 weeks gestation

**Interpretation:** Amniotic fluid lamellar body counts (LBC) above 50,000/mcL are predictive of fetal lung maturity. Amniotic fluid LBC below 15,000/mcL are suggestive of fetal lung immaturity and increased risk of neonatal respiratory distress syndrome (RDS). The main value of fetal lung maturity testing is predicting the absence of RDS. An immature test result for fetal lung maturity is less reliable in predicting the presence of RDS.(1)

**Reference Values:**
- Immature: <15,000/mcL
- Indeterminate: 15,000-50,000/mcL
- Mature: >50,000/mcL


**Clinical References:**

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**LAMO 80999**

**Lamotrigine, Serum**

**Clinical Information:** Lamotrigine (Lamictal) is approved for therapy of bipolar I disorder and a wide variety of seizure disorders including Lennox-Gastaut syndrome, primary generalized tonic-clonic seizures, and partial seizures. Its many off-label uses include treatment of migraine, trigeminal neuralgia, and treatment-refractory depression. Lamotrigine inhibits glutamate release (an excitatory amino acid) and voltage-sensitive sodium channels to stabilize neuronal membranes; it also weakly inhibits the 5-HT3 (serotonin) receptor. Lamotrigine oral bioavailability is very high (approximately 98%). The drug is metabolized by glucuronic acid conjugation to inactive metabolites. The half-life is 25 to 33 hours in adults, but decreases with concurrent use of phenytoin or carbamazepine (13-14 hours), and increases with concomitant valproic acid therapy (59-70 hours), renal dysfunction, or hepatic impairment. The therapeutic range is relatively wide, 2.5 to 15 mcg/mL for most individuals. Common adverse effects are dizziness, ataxia, blurred or double vision, nausea, or vomiting.

**Useful For:** Monitoring serum concentration of lamotrigine Assessing compliance Adjusting lamotrigine dose in patients receiving other anticonvulsant drugs which interact pharmacokinetically with lamotrigine.
Interpretation: The serum concentration should be interpreted in the context of the patient's clinical response and may provide useful information in patients showing poor response (noncompliance?) or adverse effects, particularly when lamotrigine is co-administered with other anticonvulsant drugs. While most patients show response to the drug when the trough concentration is in the range of 2.5 to 15.0 mcg/mL, and show signs of toxicity when the peak serum concentration is greater than 20 mcg/mL, some patients can tolerate peak concentrations as high as 70 mcg/mL.

Reference Values:
Patients receiving therapeutic doses usually have lamotrigine concentrations of 2.5-15.0 mcg/mL.


Langerin Immunostain, Technical Component Only

Clinical Information: Langerhans cells are specialized antigen-presenting cells residing in the skin, usually as scattered cells along the dermal-epidermal junction. Langerin is expressed in both normal and neoplastic Langerhans cells, and is specifically associated with the assembly of Birbeck granules in these cells. Langerin positivity also has been noted in lymph node sinuses and hepatic sinusoids, in which CD1a is negative.

Useful For: Visualization of normal and neoplastic Langerhans cells

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Langust (Lobster), IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
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</table>

Reference values apply to all ages.


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**LAT Immunostain, Technical Component Only**

**Clinical Information:** Linker for activation of T cells (LAT) is a transmembrane protein that plays an important role in linking engagement of the T-cell receptor (TCR) to biochemical events of T-cell activation. LAT is expressed on most T cells but is not expressed on B cells, macrophages/monocytes, dendritic cells, or epithelial cells.

**Useful For:** Distinguishing T-cell subsets and helping to classify T-cell lymphomas.

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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LATI 70632

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  Page 1342
Latex, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>
| 6     | > 100    | Strongly positive Reference values apply to all ages.


LDL a-High Density Cholesterol

Reference Values: Only orderable as part of a profile. For more information see LDLD / LDL Cholesterol (Beta-Quantification), Serum.

LDL Cholesterol (Beta-Quantification), Serum

Clinical Information: Low-density lipoprotein cholesterol (LDL-C) is widely recognized as an
established cardiovascular risk marker predicated on results from numerous clinical trials that demonstrate the ability of LDL-C to independently predict development and progression of coronary heart disease. In the United States, LDL-C remains the primary focus for cardiovascular risk assessment and evaluation of pharmacologic effectiveness. There have been considerable educational efforts invested and directed towards physicians, laboratorians, allied health staff, and the general public regarding LDL-C and strategies to lower LDL-C for reduction of cardiovascular risk. Low-density lipoproteins are a heterogeneous population of lipid particles classically defined as having a density of 1.006 to 1.063 kg/L obtained by preparative ultracentrifugation. The gold standard beta-quantification (beta-quant or BQ) method combines ultracentrifugation with precipitation and yields a collective quantitative measurement of LDL-C, intermediate-density lipoprotein cholesterol (IDL-C), and lipoprotein(a) (Lp[a]) cholesterol. In practice, LDL-C is most commonly reported using the Friedewald equation (LDL-C=TC-HDL-TG/5). Importantly, there are significant shortcomings and limitations to the Friedewald equation. Calculated LDL-C is not accurate in patients who are nonfasting, have triglycerides greater than 400 mg/dL, or have type III hyperlipoproteinemia. The equation is particularly inaccurate once the triglycerides are above 200 mg/dL or when LDL-C is <70 mg/dL. Extremely low concentrations of LDL-C are associated with 2 genetic disorders; abetalipoproteinemia and hypobetalipoproteinemia. In both cases individuals will have very low total cholesterol and diminished or absent LDL-C, apolipoprotein B (apoB) (APLB / Apolipoprotein B, Plasma) and very low-density lipoprotein cholesterol (VLDL-C). Patients may exhibit clinical signs and symptoms of polyneuropathy, intestinal fat malabsorption, hepatosteatosis, and fat soluble vitamin deficiencies (VAE / Vitamin A and Vitamin E, Serum).

Useful For: Evaluation of cardiovascular risk Assessment of low-density lipoprotein C (LDL-C) in patients with hypertriglyceridemia, type III hyperlipoproteinemia/dysbetalipoproteinemia, or when an accurate gold standard determination of LDL-C is required Diagnosis of familial hypobetalipoproteinemia and abetalipoproteinemia

Interpretation: The optimal concentration for LDL cholesterol in primary prevention depends on individual patient risk. Risk factors include: family history of coronary heart disease (CHD), hypertension, cigarette smoking, obesity, diabetes mellitus, and low HDL cholesterol, among others. Consideration of drug treatment is recommended for patients with LDL cholesterol >190 mg/dL. Values <80 mg/dL indicate hypobetalipoproteinemia. Complications due to fat malabsorption may be present in affected individuals. Undetectable LDL-C is highly suggestive of abetalipoproteinemia. Related polyneuropathy may exist in affected individuals.

Reference Values:
The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for LDL-C in adults (ages 18 years and up):
- Desirable: <100 mg/dL
- Above Desirable: 100-129 mg/dL
- Borderline high: 130-159 mg/dL
- High: 160-189 mg/dL
- Very high: > or =190 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for LDL-C in children and adolescents (ages 2-17 years):
- Acceptable: <110 mg/dL
- Borderline high: 110-129 mg/dL
- High: > or =130 mg/dL

FLDL

LDL Cholesterol, Direct

**Interpretation:** CHD Risk Factors: +1 Age: Men, 45 years and older Women, 55 years and older or premature menopause without estrogen therapy +1 Family history of premature CHD +1 Current smoking +1 Hypertension +1 Diabetes mellitus +1 Low HDL Cholesterol: 39 mg/dL or less - 1 High HDL Cholesterol: 60 mg/dL or greater LDL Cholesterol: Therapeutic goal 99 mg/dL or less if CHD is present (Optional 69 mg/dL or less) 129 mg/dL or less if no CHD and two or more risk factors 159 mg/dL or less if no CHD (Circulation 2004; 110:227-39)

**Reference Values:**

<table>
<thead>
<tr>
<th>Age</th>
<th>Desirable</th>
<th>Borderline</th>
<th>Higher Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 â€“ 19 years</td>
<td>109 mg/dL or less</td>
<td>110 â€“ 129 mg/dL</td>
<td>130 mg/dL or greater</td>
</tr>
<tr>
<td>20 years and older</td>
<td>129 mg/dL or less (99 mg/dL or less if patient has CHD)</td>
<td>130 â€“ 159 mg/dL</td>
<td>160 mg/dL or greater</td>
</tr>
</tbody>
</table>

PBUO

Lead Occupational Exposure, Random, Urine

**Clinical Information:** Lead toxicity primarily affects the gastrointestinal, neurologic, and hematopoietic systems. Increased urine lead concentration per gram of creatinine indicates significant lead exposure. Measurement of urine lead concentration per gram of creatinine before and after chelation therapy has been used as an indicator of significant lead exposure. An increase in lead concentration per gram of creatinine in the postchelation specimen of up to 6 times the concentration in the prechelation specimen is normal. Blood lead is the best clinical correlate of toxicity. For additional information, see PBDB / Lead with Demographics, Blood.

**Useful For:** Detecting clinically significant lead exposure due to occupational exposure

**Interpretation:** Urinary excretion of less than 4 mcg/g creatinine is not associated with any significant lead exposure. Urinary excretion of more than 4 mcg/g creatinine is usually associated with pallor, anemia, and other evidence of lead toxicity.

**Reference Values:**

Biological Exposure Index (BEI): <150 mcg/g creatinine


PBZP

Lead Profile Occupational Exposure, Blood

**Clinical Information:** Lead is a heavy metal commonly found in man's environment that can be an acute and chronic toxin. Lead was banned from household paints in 1978, but is still found in paint produced for nondomestic use and in artistic pigments. Ceramic products available from noncommercial suppliers (such as local artists) often contain significant amounts of lead that can be leached from the ceramic by weak acids such as vinegar and fruit juices. Lead is found in dirt from areas adjacent to homes painted with lead-based paints and highways where lead accumulates from use of leaded gasoline. Use of leaded gasoline has diminished significantly since the introduction of unleaded gasolines that have been required in personal automobiles since 1972. Lead is found in soil near abandoned industrial sites where lead may have been used. Water transported through lead or lead-soldered pipe will contain some lead with higher concentrations found in water that is weakly acidic. Some foods (for example: moonshine distilled in lead pipes) and some traditional home medicines contain lead. Lead expresses its toxicity by several mechanisms. It avidly inhibits
aminolevulinic acid dehydratase (ALA-D) and ferrochelatase, 2 of the enzymes that catalyze synthesis of heme; the end result is decreased hemoglobin synthesis resulting in anemia. Lead also is an electrophile that avidly forms covalent bonds with the sulfhydryl group of cysteine in proteins. Thus, proteins in all tissues exposed to lead will have lead bound to them. The most common sites affected are epithelial cells of the gastrointestinal tract and epithelial cells of the proximal tubule of the kidney. The typical diet in the United States contributes 1 to 3 mcg of lead per day, of which 1% to 10% is absorbed; children may absorb as much as 50% of the dietary intake, and the fraction of lead absorbed is enhanced by nutritional deficiency. The majority of the daily intake is excreted in the stool after direct passage through the gastrointestinal tract. While a significant fraction of the absorbed lead is rapidly incorporated into bone and erythrocytes, lead ultimately distributes among all tissues, with lipid-dense tissues such as the central nervous system being particularly sensitive to organic forms of lead. All absorbed lead is ultimately excreted in the bile or urine. Soft-tissue turnover of lead occurs within approximately 120 days. Avoidance of exposure to lead is the treatment of choice. However, chelation therapy is available to treat severe disease. Oral dimercaprol may be used in the outpatient setting except in the most severe cases. Erythrocyte protoporphyrin is a biologic marker of lead toxicity. Lead inhibits several enzymes in the heme synthesis pathway and causes increased levels of RBC zinc protoporphyrin (ZPP).

**Useful For:** Detecting lead toxicity

**Interpretation:** The Centers for Disease Control and Prevention (CDC) has identified the blood lead test as the preferred test for detecting lead exposure in children. Chronic whole blood lead levels below 10 mcg/dL are often seen in children. For pediatric patients, there may be an association with blood lead values of 5 to 9 mcg/dL and adverse health effects. Follow-up testing in 3 to 6 months may be warranted. Chelation therapy is indicated when whole blood lead concentration is above 25 mcg/dL in children or above 45 mcg/dL in adults. The Occupational Safety and Health Administration (OSHA) has published the following standards for employees working in industry: -Employees with whole blood lead levels above 60 mcg/dL must be removed from workplace exposure. -Employees with whole blood lead levels above 50 mcg/dL averaged over 3 blood samplings must be removed from workplace exposure. -An employee may not return to work in a lead exposure environment until their whole blood lead level is below 40 mcg/dL. -All measurements assume hematocrit of 42% and are made in mcg/dL per OSHA requirements. Elevated zinc protoporphyrin (ZPP) levels in adults may indicate long-term (chronic) lead exposure or may be indicative of iron deficiency anemia or anemia of chronic disease.

**Reference Values:**

**LEAD**

All ages: 0.0-4.9 mcg/dL  
Critical values  
Pediatrics (≤15 years): > or =20.0 mcg/dL  
Adults (> or ≥16 years): > or =70.0 mcg/dL

**ZINC PROTOPORPHYRIN**

<100 mcg/dL  
All measurements assume hematocrit of 42% and are made in mcg/dL per OSHA requirements.

**Clinical References:**  
Lead, 24 Hour, Urine

Clinical Information: Increased urine lead excretion rate indicates significant lead exposure. Measurement of urine lead excretion rate before and after chelation therapy has been used as an indicator of lead exposure. An increase in lead excretion rate in the postchelation specimen of up to 6 times the rate in the prechelation specimen is normal. Blood lead is the best clinical correlate of toxicity. For additional information, see PBDB / Lead with Demographics, Blood.

Useful For: Detecting clinically significant lead exposure in 24-hour specimens

Interpretation: Urinary excretion of less than 125 mcg of lead per 24 hours is not associated with any significant lead exposure. Urinary excretion of more than 125 mcg of lead per 24 hours is usually associated with pallor, anemia, and other evidence of lead toxicity.

Reference Values:
0-17 years: not established
> or =18 years: <1 mcg/24 hour


Lead, Capillary, with Demographics, Blood

Clinical Information: Lead is a heavy metal commonly found in man's environment that can be an acute and chronic toxin. Lead was banned from household paints in 1978, but is still found in paint produced for nondomestic use and in artistic pigments. Ceramic products available from noncommercial suppliers (such as local artists) often contain significant amounts of lead that can be leached from the ceramic by weak acids such as vinegar and fruit juices. Lead is found in dirt from areas adjacent to homes painted with lead-based paints and highways where lead accumulates from use of leaded gasoline. Use of leaded gasoline has diminished significantly since the introduction of nonleaded gasolines that have been required in personal automobiles since 1972. Lead is found in soil near abandoned industrial sites where lead may have been used. Water transported through lead or lead-soldered pipe will contain some lead with higher concentrations found in water that is weakly acidic. Some foods (eg, moonshine distilled in lead pipes) and some traditional home medicines contain lead. Lead expresses its toxicity by several mechanisms. It avidly inhibits aminolevulinic acid dehydratase and ferrochelatase, 2 of the enzymes that catalyze synthesis of heme; the end result is decreased hemoglobin synthesis resulting in anemia. Lead also is an electrophile that avidly forms covalent bonds with the sulphydryl group of cysteine in proteins. Thus, proteins in all tissues exposed to lead will have lead bound to them. The most common sites affected are epithelial cells of the gastrointestinal tract and epithelial cells of the proximal tubule of the kidney. The typical diet in the United States contributes 1 to 3 mcg of lead per day, of which 1% to 10% is absorbed; children may absorb as much as 50% of the dietary intake, and the fraction of lead absorbed is enhanced by nutritional deficiency. The majority of the daily intake is excreted in the stool after direct passage through the gastrointestinal tract. While a significant fraction of the absorbed lead is rapidly incorporated into bone and erythrocytes, lead ultimately distributes among all tissues, with lipid-dense tissues such as the central nervous system being particularly sensitive to organic forms of lead. All absorbed lead is ultimately excreted in the bile or urine. Soft-tissue turnover of lead occurs within approximately 120 days. Avoidance of exposure to lead is the treatment of choice. However, chelation therapy is available to treat severe disease. Oral dimercaprol may be used in the outpatient setting except in the most severe cases.

Useful For: Detecting lead toxicity with capillary collections
**Interpretation:** The 95th percentile of the gaussian distribution of whole blood lead concentration in a population of unexposed adults is below 6 mcg/dL. For pediatric patients, there may be an association with blood lead values of 5 to 9 mcg/dL and adverse health effects. Follow-up testing in 3 to 6 months may be warranted. Chelation therapy is indicated when whole blood lead concentration is above 25 mcg/dL in children or above 45 mcg/dL in adults. The Occupational Safety and Health Administration has published the following standards for employees working in industry: -Employees with a single whole blood lead result greater than 60 mcg/dL must be removed from workplace exposure. -Employees with whole blood lead levels greater than 50 mcg/dL averaged over 3 blood specimens must be removed from workplace exposure. -An employee may not return to work in a lead exposure environment until their whole blood lead level is less than 40 mcg/dL.

**Reference Values:**
- All ages: 0.0-4.9 mcg/dL
- Critical values
  - Pediatrics (< or =15 years): > or =20.0 mcg/dL
  - Adults (> or =16 years): > or =70.0 mcg/dL

**Clinical References:**

**Lead, Hair**

**Clinical Information:** Hair analysis for lead can be used to corroborate blood analysis or to document past lead exposure. If the hair is collected and segmented in a time sequence (based on length from root), the approximate time of exposure can be assessed.

**Useful For:** Detecting lead exposure in hair specimens

**Interpretation:** Normal hair lead content is below 5.0 mcg/g. Hair lead content above 10.0 mcg/g indicates significant lead exposure.

**Reference Values:**
- 0.0-3.9 mcg/g of hair

**Clinical References:**
1. Strumylaite L, Ryselis S, Kregzdyte R: Content of lead in human hair from people exposed to lead. Int J Hyg Environ Health 2004;207:345-351

**Lead, Nails**

**Clinical Information:** Nail analysis of lead can be used to corroborate blood analysis.

**Useful For:** Detecting lead exposure in nail specimens

**Interpretation:** Normally, the nail lead content is below 4.0 mcg/g. Nail lead content above 10.0 mcg/g indicates significant lead exposure.

**Reference Values:**
- 0.0-3.9 mcg/g of nails

**Clinical References:**
1. Strumylaite L, Ryselis S, Kregzdyte R: Content of lead in human hair from people exposed to lead. Int J Hyg Environ Health 2004;207:345-351
Reference values apply to all ages.


**Lead, Venous, with Demographics, Blood**

**Clinical Information:** Lead is a heavy metal commonly found in man’s environment that can be an acute and chronic toxin. Lead was banned from household paints in 1978, but is still found in paint produced for nondomestic use and in artistic pigments. Ceramic products available from noncommercial suppliers (such as local artists) often contain significant amounts of lead that can be leached from the ceramic by weak acids such as vinegar and fruit juices. Lead is found in dirt from areas adjacent to homes painted with lead-based paints and highways where lead accumulates from use of leaded gasoline. Use of leaded gasoline has diminished significantly since the introduction of nonleaded gasolines that have been required in personal automobiles since 1972. Lead is found in soil near abandoned industrial sites where lead may have been used. Water transported through lead or lead-soldered pipe will contain some lead with higher concentrations found in water that is weakly acidic. Some foods (eg, moonshine distilled in lead pipes) and some traditional home medicines contain lead. Lead expresses its toxicity by several mechanisms. It avidly inhibits aminolevulinic acid dehydratase and ferrochelatase, 2 of the enzymes that catalyze synthesis of heme; the end result is decreased hemoglobin synthesis resulting in anemia. Lead also is an electrophile that avidly forms covalent bonds with the sulphydryl group of cysteine in proteins. Thus, proteins in all tissues exposed to lead will have lead bound to them. The most common sites affected are epithelial cells of the gastrointestinal tract and epithelial cells of the proximal tubule of the kidney. The typical diet in the United States contributes 1 to 3 mcg of lead per day, of which 1% to 10% is absorbed; children may absorb as much as 50% of the dietary intake, and the fraction of lead absorbed is enhanced by nutritional deficiency. The majority of the daily intake is excreted in the stool after direct passage through the gastrointestinal tract. While a significant fraction of the absorbed lead is rapidly incorporated into bone and erythrocytes, lead ultimately distributes among all tissues, with lipid-dense tissues such as the central nervous system being particularly sensitive to organic forms of lead. All absorbed lead is ultimately excreted in the bile or urine. Soft-tissue turnover of lead occurs within approximately 120 days. Avoidance of exposure to lead is the treatment of choice. However, chelation therapy is available to treat severe disease. Oral dimercaprol may be used in the outpatient setting except in the most severe cases.

**Useful For:** Detecting lead toxicity

**Interpretation:** The 95th percentile of the gaussian distribution of whole blood lead concentration in a population of unexposed adults is below 6 mcg/dL. For pediatric patients, there may be an association with blood lead values of 5 to 9 mcg/dL and adverse health effects. Follow-up testing in 3 to 6 months may be warranted. Chelation therapy is indicated when whole blood lead concentration is above 25 mcg/dL in children or above 45 mcg/dL in adults. The Occupational Safety and Health Administration has published the following standards for employees working in industry: -Employees with a single whole blood lead result greater than 60 mcg/dL must be removed from workplace exposure. -Employees with whole blood lead levels greater than 50 mcg/dL averaged over 3 blood specimens must be removed from workplace exposure. -An employee may not return to work in a lead exposure environment until their whole blood lead level is less than 40 mcg/dL.

**Reference Values:**

All Ages: 0.0-4.9 mcg/dL

Critical values

Pediatrics (< or =15 years): > or =20.0 mcg/dL

Adults (> or =16 years): > or =70.0 mcg/dL
**Clinical References:**


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**Lead/Creatinine Ratio, Random, Urine**

**Clinical Information:** Increased urine lead concentration per gram of creatinine indicates significant lead exposure. Measurement of urine lead concentration per gram of creatinine before and after chelation therapy have been used as an indicator of significant lead exposure. An increase in lead concentration per gram of creatinine in the postchelation specimen of up to 6 times the concentration in the prechelation specimen is normal. Blood lead is the best clinical correlate of toxicity. For additional information, see PBBD / Lead with Demographics, Blood.

**Useful For:** Detecting clinically significant lead exposure, a toxic heavy metal, in random urine specimens

**Interpretation:** Urinary excretion of less than 4 mcg/g creatinine is not associated with any significant lead exposure. Urinary excretion greater than 4 mcg/g creatinine is usually associated with pallor, anemia, and other evidence of lead toxicity.

**Reference Values:**

- 0-17 years: not established
- > or =18 years: <2 mcg/g creatinine

**Clinical References:**


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**Lead/Creatinine Ratio, Urine**

**Clinical Information:** Increased urine lead concentration per gram of creatinine indicates significant lead exposure. Measurement of urine lead concentration per gram of creatinine before and after chelation therapy have been used as an indicator of significant lead exposure. An increase in lead concentration per gram of creatinine in the postchelation specimen of up to 6 times the concentration in the prechelation specimen is normal. Blood lead is the best clinical correlate of toxicity. For additional information, see PBBD / Lead with Demographics, Blood.

**Useful For:** Detecting clinically significant lead exposure in random urine specimens

**Interpretation:** Urinary excretion of less than 4 mcg/g creatinine is not associated with any significant lead exposure. Urinary excretion greater than 4 mcg/g creatinine is usually associated with pallor, anemia, and other evidence of lead toxicity.

**Reference Values:**

Only orderable as part of a profile. See PBRCR / Lead/Creatinine Ratio, Random, Urine or HMCRU / Heavy Metal/Creatinine Ratio, with Reflex, Urine.

**Clinical References:**

LEFLUNOMIDE METABOLITE (THERIFLUNOMIDE), SERUM

Clinical Information: Leflunomide is a disease-modifying antirheumatic drug approved for therapy of rheumatoid arthritis and used off-label to reduce viral nephritis in renal transplant. It is a prodrug: rapid and complete metabolism converts leflunomide to its active metabolite, teriflunomide (also called A77 1726), which acts by inhibiting pyrimidine synthesis. Teriflunomide has a very long half-life, on average >2 weeks. There is marked interindividual variability in leflunomide pharmacokinetics, thus therapeutic monitoring of serum teriflunomide concentrations may be helpful in optimizing therapy. Therapeutic targets remain only loosely defined and appear to vary depending on the purpose of therapy, but serum teriflunomide concentrations >40 mcg/mL have been associated with better clinical outcomes. Due to the long half-life, serum specimens for therapeutic monitoring may be drawn at any point in the dosing cycle, although trough (immediately before next schedule dose) sampling is preferred for consistency. Adverse reactions to leflunomide do not correlate well with serum drug concentration, but include diarrhea, hypertension, and liver toxicity. Enhanced elimination of the drug may be required in patients who are or who wish to become pregnant, or who are experiencing toxicity; teriflunomide can persist up to 2 years after ceasing therapy unless elimination is accelerated. This can be accomplished through use of activated charcoal or a bile acid sequestrant such as cholestyramine, reducing the half-life of teriflunomide to approximately 1 day. Serum concentrations <0.020 mcg/mL (<20 ng/mL) on 2 independent tests at least 2 weeks apart are preferred for patients anticipating pregnancy to minimize the potential risk of teratogenesis associated with the drug.

Useful For: Therapeutic monitoring of patients actively taking leflunomide Assessment of elimination in patients requiring enhanced elimination of the drug

Interpretation: Therapy: clinical targets for serum teriflunomide (leflunomide metabolite) concentrations are still being determined, but levels >40 mcg/mL appear to correlate with better outcome. Elimination: serum concentrations <0.020 mcg/mL (20 ng/mL) are preferred to minimize potential teratogenesis for patients considering pregnancy.

Reference Values:
Therapeutic: >40 mcg/mL
Elimination: <0.020 mcg/mL

Clinical References:

LEGIONELLA ANTIGEN, URINE

Clinical Information: Legionnaires disease, named after the outbreak in 1976 at the American Legion convention in Philadelphia, is caused by Legionella pneumophila and is an acute febrile respiratory illness ranging in severity from mild illness to fatal pneumonia. Since that time, it has been recognized that the disease occurs in both epidemic and endemic forms, and that sporadic cases are not readily differentiated from other respiratory infections by clinical symptoms. It is estimated that about 25,000 to 100,000 Legionella infections occur annually. Known risk factors include immunosuppression, cigarette smoking, alcohol consumption, and concomitant pulmonary disease. The resulting mortality rate, which ranges up to 40% in untreated immunocompetent patients, can be lowered if the disease can be rapidly diagnosed and appropriate antimicrobial therapy instituted early. L pneumophila is estimated to be responsible for 80% to 85% of reported cases of Legionella infections with the majority of cases being caused by L pneumophila serogroup 1 alone. A variety of laboratory techniques (culture, direct fluorescent antibody, DNA probes, immunoassay, antigen detection), using a
variety of specimen types (respiratory specimens, serum, urine), have been used to help diagnose Legionella pneumonia. Respiratory specimens are preferred. Unfortunately, one of the presenting signs of Legionnaires disease is the relative lack of productive sputum. This necessitates the use of invasive procedures to obtain adequate specimens (eg, bronchial washing, transtracheal aspirate, lung biopsy) in many patients. Serology may also be used, but is often retrospective in nature. It was shown as early as 1979 that a specific soluble antigen was present in the urine of patients with Legionnaires disease.(1) The presence of Legionella antigen in urine makes this an ideal specimen for collection, transport, and subsequent detection in early, as well as later, stages of the disease. The antigen may be detectable in the urine as early as 3 days after onset of symptoms.

**Useful For:** An adjunct to culture for the presumptive diagnosis of past or current Legionnaires disease (Legionella pneumophila serogroup 1)

**Interpretation:** Positive Presumptive positive for Legionella pneumophila serogroup 1 antigen in urine, suggesting current or past infection. Culture is recommended to confirm infection. Negative Presumptive negative for L pneumophila serogroup 1 antigen in urine, suggesting no recent or current infection. Infection with Legionella cannot be ruled out because: -Other serogroups (other than serogroup 1, which is detected by this assay) and other Legionella species (other than L pneumophila) can cause disease -Antigen may not be present in urine in early infection -The level of antigen may be below the detection limit of the test Legionella culture is recommended for cases of suspected Legionella pneumonia due to organisms other than L pneumophila serogroup 1.

**Reference Values:**

- Negative

**Clinical References:**


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**Legionella Culture**

**Clinical Information:** The Legionellaceae are ubiquitous in natural fresh water habitats, allowing them to colonize man-made water supplies, which may then serve as the source for human infections. Legionella pneumophila and the related species, Legionella bozemanii, Legionella dumoffii, Legionella gormanii, Legionella micdadei, Legionella longbeachae, and Legionella jordanis have been isolated from patients with pneumonia (Legionnaires disease). The organism has been isolated from lung tissue, bronchoalveolar lavage, pleural fluid, transtracheal aspirates, and sputum. The signs, symptoms, and radiographic findings of Legionnaires disease are generally nonspecific.

**Useful For:** Diagnosis of Legionnaires disease Because examination by rapid PCR increases sensitivity and provides faster results, Mayo Medical Laboratories strongly recommends also ordering LEGRP / Legionella species, Molecular Detection, PCR.

**Interpretation:** Identification of Legionella species from respiratory specimens provides a definitive diagnosis of Legionnaires disease. Organisms isolated are identified as Legionella species via MALDI-TOF MS and/or 16S rRNA gene sequencing.

**Reference Values:**

- No growth

**Clinical References:**

Legionella pneumophila (Legionnaires Disease), Antibody, Serum

**Clinical Information:** Legionella pneumophila may cause pulmonary disease in both normal and immunocompetent hosts. The disease may occur sporadically in the form of community acquired pneumonia and in epidemics. Pneumonia (often referred to as Legionnaires disease) occurs more frequently in severely immunosuppressed individuals; a milder form of the illness, referred to as Pontiac fever, is more prevalent in normal hosts. Extrapulmonary infection with Legionella pneumophila is rare. Legionnaires disease, Pontiac fever, and extrapulmonary infection have been collectively referred to as legionellosis. Approximately 85% of the documented cases of legionellosis have been caused by Legionella pneumophila. Serogroups 1 and 6 of Legionella pneumophila, by themselves, account for up to 75% of cases of legionellosis. The definitive diagnosis of Legionella pneumophila is made by isolation of the organism on specialized culture medium (buffered charcoal yeast extract agar). Pulmonary secretions can be directly examined using a direct fluorescent antibody procedure, but the sensitivity of this method is low (25%-70%). Often it is difficult for the patient to produce pulmonary secretion (sputum) for examination, the pneumonia is frequently interstitial and sputum is scant. In the absence of invasive procedures (eg, bronchial alveolar lavage), urine evaluation for Legionella pneumophila antigen or indirect serological (antibody) methods may be useful.

**Useful For:** Evaluation of possible legionellosis (Legionnaires disease, Pontiac fever, extrapulmonary legionella infection caused by Legionella pneumophila)

**Interpretation:** A negative result indicates that IgG, IgA, and IgM antibody to Legionella pneumophila serogroups 1-6 was not detected. Negative results do not exclude Legionella infection. It may require 4 to 8 weeks to develop a detectable antibody response; serum specimens taken early in the course of infection may not yet have significant antibody titers. Furthermore, antibody levels can fall to undetectable levels within a month of infection, early antibiotic therapy may suppress antibody response, and some individuals may not develop antibodies above detectable limits. Some culture-positive cases of Legionella do not develop Legionella antibody. Positive results are suggestive of Legionella infection; however, a single positive result only indicates immunologic exposure at some time. It does not distinguish between previous or current infection. The level of antibody response may not be used to determine active infection. Other laboratory procedures or additional clinical information are necessary to establish a diagnosis. Specimens with equivocal results are retested prior to reporting. Repeat testing on a second specimen should be considered in patients with equivocal results, if clinically indicated.

**Reference Values:**

- Negative

Reference values apply to all ages.

**Clinical References:**

Legionella species, Molecular Detection, PCR

**Clinical Information:** Legionnaires disease was first recognized during a pneumonia outbreak at the Legionnaires convention in Philadelphia in 1976. Investigators with the CDC isolated a novel, gram-negative bacillus, later named Legionella pneumophila. It is now widely recognized that L pneumophila (and other members of the genus Legionella) cause Legionnaires disease.

**Useful For:** Sensitive and rapid diagnosis of pneumonia caused by Legionella species

**Interpretation:** A positive PCR result for the presence of a specific sequence found within the
Legionella 5S rRNA gene indicates the presence of a Legionella species DNA, which may be due to Legionella infection or environmental/water Legionella DNA in the specimen. A negative PCR result indicates the absence of detectable Legionella DNA in the specimen, but does not rule-out legionellosis as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of Legionella species in quantities less than the limit of detection of the assay.

Reference Values:
Not applicable

Clinical References:

Leishmaniasis (Visceral) Antibody, Serum

Clinical Information: Visceral leishmaniasis (kala azar) is a disseminated intracellular protozoal infection that targets primarily the reticuloendothelial system (liver, spleen, bone marrow) and is caused by Leishmania donovani, L chagasi, or L infantum (L donovani complex). Transmission is by the bite of sandflies. Clinical symptoms include fever, weight loss, and splenomegaly; pancytopenia and hypergammaglobulinemia are often present. Most (90%) new cases each year arise in rural areas of India, Nepal, Bangladesh, Sudan, and Brazil but the disease has a worldwide distribution, including the Middle East. Definitive diagnosis has required the microscopic documentation of characteristic intracellular amastigotes in stained smears from culture of aspirates of tissue (spleen, lymph node) or bone marrow. The detection of serum antibodies to the recombinant K39 antigen of L donovani is an alternative noninvasive sensitive (95%-100%) method for the diagnosis of active, visceral leishmaniasis.

Useful For: Diagnosis of active visceral leishmaniasis

Interpretation: A positive result is consistent with a diagnosis of active visceral leishmaniasis.

Reference Values:
Negative
Reference values apply to all ages.

Clinical References:

FLEMG

Lemon IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
**Lemon, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
</tr>
</tbody>
</table>


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**Lentil IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be
taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Lentil, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<th>Class</th>
<th>kU/L</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
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<td>Equivocal</td>
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<tr>
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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
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**Lepidoglyphus destructor, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and...
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**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tbody>
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Reference values apply to all ages.


**FLEP 91339**

**Leptin**

**Reference Values:**

<table>
<thead>
<tr>
<th>Units: ng/mL</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Adults (BMI=22)</td>
</tr>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Females</td>
</tr>
</tbody>
</table>

Contact laboratory for other BMI reference ranges.

**LEPDT 65183**

**Leptospira, IgM, Serum**

**Clinical Information:** Leptospirosis is a zoonotic disease of worldwide prevalence, though the majority of infections occur in warm, tropical climates. Wild mammals, typically rodents, are the primary, natural reservoir for pathogenic strains of Leptospira, however, domestic animals (eg, dogs) also represent a major source of human infection. Leptospira are Gram-negative spirochetes with at least 20 different species in the genus. Of these, at least 9 species are considered pathogenic, including the most common agent of leptospirosis, Leptospira interrogans. Transmission occurs through indirect
human contact (e.g., via mucous membranes or abraded skin) with water, food, or soil contaminated with animal urine containing the Leptospira spirochetes. Following infection, the incubation period can range from 3 to 30 days depending on the inoculum dose and immune status of the individual. The clinical manifestations of leptospirosis can vary, ranging from a mild, flu-like illness (e.g., headache, malaise, fever, arthralgia, fatigue) to fulminant disease, with severe liver and kidney involvement. The latter manifestation was previously referred to as Weil disease. Leptospira organisms may be found in the blood at the onset of disease and can persist for approximately 1 week. Subsequently, spirochetes may be found in the urine and can persist for 2 to 3 months; however, shedding may be intermittent and the numbers of organisms present may be low. While Leptospira can be grown in culture, this is a fastidious organism and requires immediate transport to the laboratory. Additionally, detectable growth requires prolonged incubation (1-6 weeks), limiting the utility of culture for acute diagnosis. For this reason, serologic detection for antibodies to Leptospira remains the method of choice for rapid diagnosis. IgM-class antibodies to this spirochete are detectable by day 6 of illness and remain detectable for 2 to 3 months following symptom onset.

**Useful For:** Aids in the diagnosis of leptospirosis

**Interpretation:** Positive: IgM antibodies to Leptospira species detected suggesting recent infection. Antibody presence alone cannot be used to definitively diagnose acute infection, as antibodies from a prior exposure or infection may remain detectable for a prolonged period of time. Borderline: Result should be interpreted with caution. Additional testing of a second, convalescent specimen is recommended. If the specimen remains borderline reactive, a second serological method should be considered if leptospirosis infection is still suspected. Negative: No IgM antibodies to Leptospira detected. Since antibodies may not be present or may be present at undetectable levels during early disease, repeat testing of a convalescent sample collected in 2 to 3 weeks is recommended.

**Reference Values:**

Negative

**Clinical References:**
3. Package Insert: ImmunoDot Leptospira IgM, GenBio, San Diego, CA; Version 4.0

**FLETG**

**Lettuce IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**LETT**

**Lettuce, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical
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**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


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**Leukemia and Lymphoma Phenotyping, Technical Only**

**Clinical Information:** Diagnostic hematopathology has become an increasingly complex subspecialty, particularly with neoplastic disorders of blood and bone marrow. While morphologic assessment of blood smears, bone marrow smears, and tissue sections remains the cornerstone of lymphoma and leukemia diagnosis and classification, immunophenotyping is a very valuable and important complementary tool. Immunophenotyping hematopoietic specimens can help resolve many differential diagnostic problems posed by the clinical or morphologic features. This test is appropriate for hematopoietic specimens only. This is a technical only test and does not include interpretation unless reflex testing is performed. At any point, clients may request to have a Mayo Clinic hematopathologist provide an interpretation at an additional charge.

**Useful For:** Evaluating lymphocytoses of undetermined etiology Identifying B- and T-cell lymphoproliferative disorders involving blood and bone marrow Distinguishing acute lymphoblastic leukemia from acute myeloid leukemia (AML) Immunologic subtyping of acute leukemias Distinguishing reactive lymphocytes and lymphoid hyperplasia from malignant lymphoma Distinguishing between malignant lymphoma and acute leukemia Phenotypic subclassification of B- and T-cell chronic lymphoproliferative disorders, including chronic lymphocytic leukemia, mantle cell lymphoma, and hairy cell leukemia Recognizing AML with minimal morphologic or cytochemical evidence of differentiation Recognizing monoclonal plasma cells

**Interpretation:** Report will include a summary of the procedure.
Reference Values:
Not applicable


Leukemia/Lymphoma Immunophenotyping by Flow Cytometry

Clinical Information: Diagnostic hematopathology has become an increasingly complex subspecialty, particularly with neoplastic disorders of blood and bone marrow. While morphologic assessment of blood smears, bone marrow smears, and tissue sections remains the cornerstone of lymphoma and leukemia diagnosis and classification, immunophenotyping is a very valuable and important complementary tool. Immunophenotyping hematopoietic specimens can help resolve many differential diagnostic problems posed by the clinical or morphologic features.

Useful For: Evaluating lymphocytoses of undetermined etiology Identifying B- and T-cell lymphoproliferative disorders involving blood and bone marrow Distinguishing acute lymphoblastic leukemia (ALL) from acute myeloid leukemia (AML) Immunologic subtyping of ALL Distinguishing reactive lymphocytes and lymphoid hyperplasia from malignant lymphoma Distinguishing between malignant lymphoma and acute leukemia Phenotypic subclassification of B- and T-cell chronic lymphoproliferative disorders, including chronic lymphocytic leukemia, mantle cell lymphoma, and hairy cell leukemia Recognizing AML with minimal morphologic or cytochemical evidence of differentiation Recognizing monoclonal plasma cells

Interpretation: Report will include a morphologic description, a summary of the procedure, the percent positivity of selected antigens, and an interpretive conclusion based on the correlation of the clinical history with the morphologic features and immunophenotypic results.

Reference Values:
An interpretive report will be provided.

This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and correlation with the morphologic features will be provided by a hematopathologist for every case.

**Leukemia/Lymphoma Immunophenotyping by Flow Cytometry, Tissue**

**Clinical Information:** Cellular immunophenotyping, characterizing cells by using antibodies directed against cell surface markers, is generally regarded as a fundamental element in establishing a diagnosis of tissue involvement by hematolymphoid malignancies, when used in conjunction with morphologic assessment. It is also an essential component in subclassification of hematolymphoid malignancies, when present.

**Useful For:** Evaluation of tissues for potential involvement by: -Chronic lymphoproliferative disorders -Malignant lymphomas -Acute lymphoblastic leukemia -Acute myelogenous leukemia

**Interpretation:** Normal tissues typically contain a mixture of B cells with polytypic surface immunoglobulin light chain expression and T cells with unremarkable expression of the T cell-associated antigens CD3, CD5, and CD7. Typically, no appreciable blast population is present by CD45 and side scatter analysis.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
expression of CD18 on neutrophils) characteristically have delayed umbilical stump separation (>30 days), infection of the umbilical stump (omphalitis), persistent leukocytosis (>15,000/microliter) in the absence of overt active infection, and severe destructive gingivitis with periodontitis and associated tooth loss, and alveolar bone resorption. Patients with the moderate phenotype of LAD-1 (1%-30% of normal expression of CD18 on neutrophils) tend to be diagnosed later in life. Normal umbilical separation, lower risk of life-threatening infections, and longer life expectancy are common in these patients. However, leukocytosis, periodontal disease, and delayed wound healing are still very significant clinical features. Patients with LAD-1 (and other primary immunodeficiency diseases) are unlikely to remain undiagnosed in adulthood. Consequently, this test should not be typically ordered in adults for LAD-1. However, it may be also used to assess immune competence by determining CD18, 11a, and 11b expression.

**Useful For:** Aids in the diagnosis of leukocyte adhesion deficiency syndrome type 1, primarily in patients younger than 18 years of age CD11a, CD11b, and CD18 phenotyping

**Interpretation:** The report will include a summary interpretation of the presence or reduction in the level of expression of the individual markers (CD11a, CD11b, and CD18). Expression of the individual markers provides indirect information on the presence or absence of the CD11a/CD18 and CD11b/CD18 complexes. Specimens obtained from patients with leukocyte adhesion deficiency syndrome type 1 (LAD-1) show significant reduction (moderate phenotype) or near absence (severe phenotype) of CD18 and its associated molecules, CD11a and CD11b, on neutrophils and other leukocytes. CD11c expression also is low in LAD-1. The analytical sensitivity of the CD11c assay is insufficient to allow interpretation of CD11c surface expression. Therefore, we test only for expression of CD18, CD11a, and CD11b.

**Reference Values:**
Normal (reported as normal or absent expression for each marker)

**Clinical References:**

**LECT2 70497**

**Leukocyte Cell-Derived Chemotaxin 2 (LECT2), Immunostains Without Interpretation**

**Clinical Information:** Immunohistochemical staining for leukocyte cell-derived chemotaxin 2 (LECT2) is useful in the process of confirming amyloid subtype. Antibodies to LECT2 stain the amyloid deposits in patients with LECT2 amyloidosis. LECT2 amyloidosis typically involves the kidney, liver, and spleen.

**Useful For:** Identification and classification of amyloid subtypes in tissue

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.
Leukotriene E4, Urine

Clinical Information: Leukotrienes (LTs) are eicosanoids generated from arachidonic acid via the 5-lipoxygenase pathway. Leukotriene E4 (LTE4) is the stable end product of this pathway and therefore regarded as a biomarker of total cysteinyl leukotriene (cys-LT) production. Assessment of LTE4 in urine allows for noninvasive specimen collection and avoids artifactual formation of LTs during phlebotomy. Generation of LTE4 occurs nonspecifically from active mast cells, basophils, eosinophils, and macrophages, and modulated through a variety of mechanisms. Elevated concentrations of LTE4 are associated with inflammatory and accelerated mast cell activation conditions, specifically in patients with systemic mast cell disease. (1) Systemic mastocytosis (SM), or systemic mast cell disease, is a myeloproliferative neoplasm which has infiltrated extracutaneous organs. Release of mast cell inflammatory mediators leads to disease symptoms including those associated with allergic and anaphylactic reactions, while increased mast cell numbers lead to organ dysfunction. Consensus diagnostic criteria for SM include 1 major criterion: imaging of the multifocal infiltrates; and 4 minor criteria: 1) identifying morphological features of >25% of mast cells from bone marrow biopsy, 2) detection of the point mutation at codon 816 in the KIT gene, 3) CD2 and/or CD25 expression in mast cells, and 4) persistently elevated serum tryptase. Diagnosis requires either 1 major plus 1 minor criterion or 3 minor criteria. (2) Measurement of urinary mast cell activation biomarkers can aid in the initial evaluation of suspected cases of systemic mast cell disease, potentially avoiding the need for imaging and bone marrow examination. Patients with SM frequently have elevated urine concentrations of LTE4(1), N-methylhistamine(3,4), and/or 2,3-dinor 11 beta-prostaglandin F2 alpha. (4) Urinary LTE4 has also demonstrated significant utility in patients with asthma and respiratory diseases. In a study of adults with mild to moderate asthma on 5-lipoxygenase inhibitors, urine LTE4 concentrations decreased approximately 40% compared to asthma control subjects, suggesting modest decreases in LTE4 production correlates with clinical improvements in asthma severity.

Useful For: An aid to evaluate patients suspected of having systemic mastocytosis

Interpretation: Elevated urinary leukotriene E4 (LTE4) concentrations >104 pg/mg creatinine are consistent with the diagnosis of systemic mast cell disease when combined with clinical signs and symptoms. Pharmacological treatment with 5-lipoxygenase inhibitors or leukotriene receptor antagonists has been shown to decrease production of LTE4. Urinary LTE4 may be used together with serum tryptase, urinary 2,3-dinor 11 beta-prostaglandin F2 alpha, and/or urinary N-methyl histamine.

Reference Values:
< or =104 pg/mg creatinine


LEV1P

Level 1 Gross only (Bill Only)

Reference Values: This test is for billing purposes only.
This is not an orderable test.

**LEV2P**
Level 2 Gross and microscopic (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

**LEV3P**
Level 3 Gross and microscopic (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

**LEV4P**
Level 4 Gross and microscopic (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

**LV4RP**
Level 4 Gross and Microscopic, RB (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

**LEV5P**
Level 5 Gross and microscopic (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

**LEV6P**
Level 6 Gross and microscopic (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

**LEVE**
Levetiracetam, Serum

Clinical Information: Levetiracetam is approved for treatment of partial, myoclonic, and tonic-clonic seizures, and is used off-label for manic states and migraine prophylaxis. Levetiracetam has very favorable pharmacokinetics with good bioavailability and rapid achievement of steady state. Its hepatic metabolism is minimal and nonoxidative, making it safe for use with hepatic enzyme inducers or inhibitors. The major metabolite is a carboxylic acid derivate, which is inactive and accounts for roughly one quarter of the administered dose. Levetiracetam is excreted renally, with a mean half-life of 7 hours in adults and slightly less than that in children. Renal dysfunction may warrant therapeutic monitoring and/or dose adjustment. Given the lack of drug interactions and favorably pharmacokinetics, the primary uses for therapeutic drug monitoring of levetiracetam are compliance assurance and management of physiological changes such as puberty, pregnancy, and aging. Toxicities associated with levetiracetam use
include decreased hematocrit and red blood cell count, decreased neutrophil count, somnolence, asthenia, and dizziness. These toxicities may be associated with blood concentrations in the therapeutic range.

**Useful For:** Monitoring serum concentration of levetiracetam, particularly in patients with renal disease Assessing compliance Assessing potential toxicity

**Interpretation:** Most individuals display optimal response to levetiracetam with serum levels 12 to 46 mcg/mL. Some individuals may respond well outside of this range, or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Toxic levels have not been well established. Therapeutic ranges are based on specimen drawn at trough (ie, immediately before the next dose).

**Reference Values:**
12.0-46.0 mcg/mL


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**FLEVO**

**90333**

**Levodopa, Serum/Plasma**

**Reference Values:**
Reporting limit determined each analysis
Steady state during chronic 3 to 8 gram p.o. dose: 0.2-3 mcg/mL plasma.

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**LIDO**

**37045**

**Lidocaine, Serum**

**Clinical Information:** Lidocaine is commonly used as a local anesthetic, but is also effective at controlling ventricular arrhythmia and ventricular fibrillation in children and adults. For cardiac therapy, optimal therapeutic response is seen when serum concentrations are between 1.5 and 5.0 mcg/mL. Lidocaine is 50% protein-bound, primarily to alpha-1-acid glycoprotein; concentrations of this protein increase after myocardial infarction, which may decrease the amount of free lidocaine and, thus, its efficacy. Lidocaine undergoes extensive first-pass hepatic metabolism and, thus, is not administered orally. It is eliminated via renal clearance, with a half-life of approximately 1.5 hours. Diseases that reduce hepatic or renal function reduce clearance and prolong elimination of lidocaine. Toxicity occurs when the concentration of lidocaine is greater than 6.0 mcg/mL and is usually associated with symptoms of central nervous system excitation, light-headedness, confusion, dizziness, tinnitus, and blurred or double vision. This can be accompanied by bradycardia and hypotension leading to cardiovascular collapse.

**Useful For:** Assessing optimal dosing during the acute management of ventricular arrhythmias following myocardial infarction or during cardiac manipulation such as surgery Assessing potential toxicity

**Interpretation:** Optimal response to lidocaine occurs when the serum concentration is between 1.5 and 5.0 mcg/mL. Toxicity is more likely when concentrations exceed 6.0 mcg/mL.

**Reference Values:**
Therapeutic: 1.5-5.0 mcg/mL
Critical value: >6.0 mcg/mL

**LMO2**

**LIM Domain Only 2 (LMO2) Immunostain, Technical Component Only**

**Clinical Information:** LIM domain only 2 (LMO2) is a transcription factor that regulates vascular and hematopoietic systems and is involved in hematolymphoid neoplasia. LMO2 is preferentially expressed by germinal center B cells and may also be expressed in erythroid and myeloid precursors and in megakaryocytes. Expression has been observed in cases of lymphoblastic and acute myeloid leukemia. It is rarely expressed in mature T, natural killer, and plasma cell neoplasms and is absent from nonhematolymphoid tissues except for endothelial cells. In the diagnosis of B-cell lymphomas, LMO2 can be useful in an immunohistochemical panel to assign a germinal center phenotype.

**Useful For:** Classification of lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**LIME**

**Lime, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Limulus Amebocyte Lysate (Endotoxin)**

**Reference Values:**

<table>
<thead>
<tr>
<th>LEVEL DETECTED</th>
<th>INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.05 EU/mL</td>
<td>None Detected</td>
</tr>
<tr>
<td>0.125 EU/mL</td>
<td>Action level for dialysis water</td>
</tr>
<tr>
<td>&lt;0.25 EU/mL</td>
<td>Maximum allowable level for dialysis water and USP acceptable limits for injectable or irrigation water</td>
</tr>
<tr>
<td>0.25 EU/mL</td>
<td>Action level for dialysis fluid</td>
</tr>
<tr>
<td>&lt;0.50 EU/mL</td>
<td>Maximum allowable level for dialysis fluid and USP acceptable limits for inhalatory water.</td>
</tr>
<tr>
<td>2.00 EU/mL</td>
<td>Acceptable upper limit for Hemodialysis reuse water.</td>
</tr>
</tbody>
</table>

The LAL is used as a quantitative test to detect gram-negative endotoxin in aqueous solutions used in patient management. The LAL assay is not recommended for serum or plasma samples due to the presence of inhibitory factors. It is essential to maintain specimen sterility and prevent false positive results from exogenous gram negative bacteria.

**Linden, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to...
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive

Reference values apply to all ages.


LPBF1
Lipase, Body Fluid
Clinical Information: Lipases are enzymes that hydrolyze glycerol esters of long-chain fatty acids and produce fatty acids and 2-acylglycerol. The pancreas is the primary source of serum lipase. Pancreatic injury results in increased serum lipase levels. Serum lipase is measured to aid in the diagnosis of pancreatitis. Peritoneal fluid: The digestive enzymes amylase and lipase can be measured in the identification of pancreatic fluid in the peritoneal cavity. Concentrations are expected to be elevated and at least several-fold times higher in fluid of pancreatic origin compared to simultaneous concentrations in serum.(1) Drain fluid: Lipase is expected to be elevated in drain fluids formed due to chronic pancreatitis or formation of a fistula following surgery.(2,3) Comparison to serum concentrations is recommended with elevations several-fold higher than blood being suggestive of the presence of pancreatic fluid in the drained cavity.(4)

Useful For: Determining whether pancreatic inflammation or pancreatic fistula may be contributing to a pathological accumulation of fluid

Interpretation: Fluids: Peritoneal, Drain -Lipase concentrations several-fold higher than serum is suggestive of the presence of pancreatic fluid in the drained cavity. All other fluids: -Body fluid lipase activity may become elevated due to the presence of pancreatic fluid in the drained cavity. Results should be interpreted in conjunction with serum lipase and other clinical findings.

Reference Values: Not applicable


FLIPR
Lipase, Random Urine
Reference Values: Adult: 4 U/L or less
**Lipase, Serum**

**Clinical Information:** Lipases are enzymes that hydrolyze glycerol esters of long-chain fatty acids and produce fatty acids and 2-acylglycerol. Bile salts and a cofactor, colipase, are required for full catalytic activity and greatest specificity. The pancreas is the primary source of serum lipase. Both lipase and colipase are synthesized in the pancreatic acinar cells and secreted by the pancreas in roughly equimolar amounts. Lipase is filtered and reabsorbed by the kidneys. Pancreatic injury results in increased serum lipase levels. Amylase measurement is used for a similar purpose. Many studies have looked at concurrent ordering of amylase and lipase in patients with abdominal pain and found lipase has slightly improved sensitivity for diagnosing acute pancreatitis and measurement of both analytes was unnecessary.

**Useful For:** Investigating pancreatic disorders, usually pancreatitis, serum specimens

**Interpretation:** In pancreatitis, lipase becomes elevated at about the same time as amylase (in 4-8 hours). But lipase may rise to a greater extent and remain elevated much longer (7-10 days) than amylase. Elevations 2 to 50 times the upper reference have been reported. The increase in serum lipase is not necessarily proportional to the severity of the attack. Normalization is not necessarily a sign of resolution.

**Reference Values:**
12-61 U/L

**Clinical References:**

**Lipid Analysis, Body Fluid**

**Clinical Information:** The presence of a chylous effusion, which results from lymphatic drainage into a body cavity, can be determined by identifying triglycerides and chylomicrons in the fluid. Catheter-related iatrogenic effusions can be identified by determining the presence of intravenous solution constituents in the fluid.

**Useful For:** Distinguishing between chylous and nonchylous effusions Identifying iatrogenic effusions

**Interpretation:** Triglyceride concentration >110 mg/dL is highly suggestive of a chylous effusion.

**Reference Values:** Not applicable

**Clinical References:**

**Lipid Panel, Fasting**

**Clinical Information:** Cardiovascular disease is the number one cause of death in the United States with an estimated 1.5 million heart attacks and 0.5 million strokes occurring annually, many in individuals who have no prior symptoms. Prevention of ischemic cardiovascular events is key. Risk factors including age, smoking status, hypertension, diabetes, cholesterol, and HDL cholesterol, are used by physicians to identify individuals likely to have an ischemic event.

**Useful For:** Evaluation of cardiovascular risk

**Interpretation:** Mayo Clinic has adopted the National Lipid Association classifications, which are included as reference values on Mayo Clinic and Mayo Medical Laboratories reports (see Reference Values). Lipids are most commonly measured to assess cardiovascular risk. Maintaining desirable concentrations of lipids lowers the risk of heart attacks or strokes. Establishing appropriate treatment
strategies and lipid goals require the results for each component of a lipid profile be considered in context with other risk factors including, age, sex, smoking status, family and personal history of heart disease.

**Reference Values:**
The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in adults ages 18 and up:

**TOTAL CHOLESTEROL**
Desirable: <200 mg/dL
Borderline high: 200-239 mg/dL
High: > or =240 mg/dL

**TRIGLYCERIDES**
Normal: <150 mg/dL
Borderline high: 150-199 mg/dL
High: 200-499 mg/dL
Very high: > or =500 mg/dL

**HDL CHOLESTEROL**
Males
> or =40 mg/dL
Females
> or =50 mg/dL

**LDL CHOLESTEROL**
Desirable: <100 mg/dL
Above desirable: 100-129 mg/dL
Borderline high: 130-159 mg/dL
High: 160-189 mg/dL
Very high: > or =190 mg/dL

**NON-HDL CHOLESTEROL**
Desirable: <130 mg/dL
Above desirable: 130-159 mg/dL
Borderline high: 160-189 mg/dL
High: 190-219
Very high: > or =220 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in children ages 2-17:

**TOTAL CHOLESTEROL**
Acceptable: <170 mg/dL
Borderline high: 170-199 mg/dL
High: > or =200 mg/dL

**TRIGLYCERIDES**
2-9 years:
Acceptable: <75 mg/dL
Borderline high: 75-99 mg/dL
High: > or =100 mg/dL
10-17 years:
Acceptable: <90 mg/dL
Borderline high: 90-129 mg/dL
High: > or =130 mg/dL
HDL CHOLESTEROL
Low HDL: <40 mg/dL
Borderline low: 40-45 mg/dL
Acceptable: >45 mg/dL

LDL CHOLESTEROL
Acceptable: <110 mg/dL
Borderline high: 110-129 mg/dL
High: > or =130 mg/dL

NON-HDL CHOLESTEROL
Acceptable: <120 mg/dL
Borderline high: 120-144 mg/dL
High: > or =145 mg/dL


Lipid Panel, Non-Fasting, Serum

Clinical Information: Cardiovascular disease is the number one cause of death in the United States with an estimated 1.5 million heart attacks and 0.5 million strokes occurring annually, many in individuals who have no prior symptoms. Prevention of ischemic cardiovascular events is key. Risk factors, including age, smoking status, hypertension, diabetes, cholesterol, and HDL cholesterol, are used by physicians to identify individuals likely to have an ischemic event.

Useful For: Evaluation of cardiovascular risk

Interpretation: Mayo Clinic has adopted the National Lipid Association classifications, which are included as reference values on Mayo Clinic and Mayo Medical Laboratories reports (see Reference Values). Lipids are most commonly measured to assess cardiovascular risk. Maintaining desirable concentrations of lipids lowers the risk of heart attacks or strokes. Establishing appropriate treatment strategies and lipid goals require the results for each component of a lipid profile to be considered in context with other risk factors including, age, sex, smoking status, family and personal history of heart disease. Nonfasting lipids are endorsed by the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines, in which a follow-up fasting sample is recommended if triglycerides exceed normal levels.

Reference Values:
The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in adults ages 18 and up:

TOTAL CHOLESTEROL
Desirable: <200 mg/dL
Borderline high: 200-239 mg/dL
High: > or =240 mg/dL

TRIGLYCERIDES
Males
<200 mg/dL
Females
<175 mg/dL
HDL CHOLESTEROL
Males
> or =40 mg/dL
Females
> or =50 mg/dL

LDL CHOLESTEROL
Desirable: <100 mg/dL
Above desirable: 100-129 mg/dL
Borderline high: 130-159 mg/dL
High: 160-189 mg/dL
Very high: > or =190 mg/dL

NON HDL CHOLESTEROL
Desirable: <130 mg/dL
Above desirable: 130-159 mg/dL
Borderline high: 160-189 mg/dL
High: 190-219
Very high: > or =220 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in children ages 2-17 years of age:

TOTAL CHOLESTEROL
Acceptable: <170 mg/dL
Borderline high: 170-199 mg/dL
High: > or =200 mg/dL

TRIGLYCERIDES
2-9 years:
Acceptable: <75 mg/dL
Borderline high: 75-99 mg/dL
High: > or =100 mg/dL
10-17 years:
Acceptable: <90 mg/dL
Borderline high: 90-129 mg/dL
High: > or =130 mg/dL

HDL CHOLESTEROL
Low HDL: <40 mg/dL
Borderline low: 40-45 mg/dL
Acceptable: >45 mg/dL

LDL CHOLESTEROL
Acceptable: <110 mg/dL
Borderline high: 110-129 mg/dL
High: > or =130 mg/dL

NON HDL CHOLESTEROL
Acceptable: <120 mg/dL
Borderline high: 120-144 mg/dL
High: > or =145 mg/dL

**Lipoprotein (a) Cholesterol, Serum**

**Clinical Information:** Lipoprotein(a) (Lp[a]) is a highly heterogeneous molecule, consisting of a low-density lipoprotein (LDL) with a highly glycosylated apolipoprotein(a) (apo[a]) covalently linked to the apolipoprotein B moiety of LDL via a single disulfate bond. Lp(a) has been associated with atherogenesis and promotion of thrombosis. Increased levels of Lp(a) have been estimated to confer a 1.5 to 3.0-fold increased risk for coronary artery disease (CAD) in many but not all studies. Apo(a) has approximately 80% structural homology with plasminogen, but does not contain the active site for fibrin cleavage. One proposed mechanism for Lp(a)'s atherogenicity is competition for binding sites with plasminogen during fibrin clot formation and the resulting inhibition of fibrinolysis. Recently a high correlation was demonstrated between Lp(a) and oxidized LDL, suggesting that the atherogenicity of Lp(a) lipoprotein may be mediated in part by associated proinflammatory oxidized phospholipids. The heterogeneity of Lp(a) arises mainly from the variable number of kringle repeats in the apo(a) portion of the molecule. Kringles are specific structural domains containing 3 intra-strand disulfide bonds that are highly homologous to similar repeats found in plasminogen. In the clinical laboratory, immunologic methods are generally used to quantify Lp(a) protein mass. Reagents for Lp(a) mass measurement are available from multiple manufacturers and although standardization efforts are underway, currently available methods are not standardized. Difficulties in standardizing Lp(a) mass measurement arise from the variability in signals produced by different reagents due to the size polymorphisms of apo(a). For this reason, some elevations of Lp(a) mass are associated with low levels of Lp(a) cholesterol. Lp(a) quantification can be done by densitometric measurement of Lp(a) cholesterol. This method measures only the cholesterol contained in the Lp(a) particles and is thus not influenced by the relative size of the apo(a) particle. Because Lp(a) cholesterol measurement is not influenced by apo(a) size, it may provide a more specific assessment of cardiovascular risk than Lp(a) mass measurement. Lp(a) cholesterol measurement may be used in concert with Lp(a) mass determination, or may be used as a stand-alone test for assessment of risk.

**Useful For:** Evaluation of increased risk for cardiovascular disease and events: -Most appropriately measured in individuals at intermediate risk for cardiovascular disease -Patients with early atherosclerosis or strong family history of early atherosclerosis without explanation by traditional risk factors should also be considered for testing -Follow-up evaluation of patients with measurable lipoprotein(a) protein (LIPA)

**Interpretation:** Patients with increased Lp(a) cholesterol values have an approximate 2-fold increased risk for developing cardiovascular disease and events. Lipoprotein-X (LpX) is an abnormal lipoprotein that appears in the sera of patients with obstructive jaundice, and is an indicator of cholestasis. The presence of LpX will be reported if noted during Lp(a) cholesterol analysis.

**Reference Values:**
Lp(a) CHOLESTEROL  
Normal: <3 mg/dL  
Suggests increased risk of coronary artery disease: > or =3 mg/dL

LpX  
Undetectable

in plasma with and without ultracentrifugation: comparison with an immunoturbidimetric lipoprotein[a]
Lipoprotein (a) cholesterol, but not Lp(a) mass, is an independent predictor of angiographic coronary
artery disease and subsequent cardiovascular events in patients referred for coronary angiography.
Circulation 2007;116:II_818

LIPA
81558

Lipoprotein (a), Serum

Clinical Information: Lipoprotein (a) (Lp[a]) consists of an LDL particle that is covalently bound
to an additional protein, apolipoprotein (a) (Apo[a]). Apo(a) has high-sequence homology with the
coaulation factor plasminogen and, like LDL, Lp(a) contains apolipoprotein B100 (ApoB). Thus, Lp(a)
is both proatherogenic and prothrombotic. Lp(a) is an independent risk factor for coronary heart disease
(CHD), ischemic stroke, and aortic valve stenosis. Lp(a) has been referred to as "the most atherogenic
lipoprotein." The mechanism of increased risk is unclear but most likely involves progression of
atherosclerotic stenosis via intimal deposition of cholesterol and promotion of thrombosis via homology
to plasminogen. Concentrations of Lp(a) particles in the blood can be expressed readily by 2 methods:
as concentrations of Lp(a) protein or as Lp(a) cholesterol. MayoC™s Cardiovascular Laboratory
Medicine measures and reports Lp(a) cholesterol individually (LPAWS / Lipoprotein [a] Cholesterol,
Serum) and as a part of the lipoprotein profile (LMPP / Lipoprotein Metabolism Profile). The
cholesterol content of Lp(a) particles varies little, and Lp(a) can contain significant proportions of the
serum cholesterol. Unlike Lp(a) cholesterol, accurate immunochemical measurement of Lp(a)-specific
protein, is complicated by the heterogeneity of Lp(a) molecular size. Due to the large number of
polymorphisms in the population any given individual can have an Apo(a) protein between 240 to 800
kDa. This heterogeneity leads to inaccuracies when results are expressed in terms of mg/dL of protein.
In addition, the degree of atherogenicity of the Lp(a) particle may depend on the molecular size of the
Lp(a)-specific protein. Serum concentrations of Lp(a) are related to genetic factors, and are largely
unaffected by diet, exercise and lipid-lowering pharmaceuticals. However, in a patient with additional
modifiable CHD risk factors, more aggressive therapy to normalize these factors may be indicated if the
Lp(a) value is also increased.

Useful For: Cardiovascular disease (CVD) risk refinement in patients with moderate or high risk
based on conventional risk factors

Interpretation: The frequency distribution of serum lipoprotein (a) (Lp[a]) concentrations is
markedly skewed toward the low end, with approximately 85% of the population having concentrations
<30 mg/dL. Lp(a) concentrations >30 mg/dL are associated with 2- to 3-fold increased risk of
cardiovascular events independent of conventional risk markers.

Reference Values:
< or =30 mg/dL
   Values >30 mg/dL may suggest increased risk of coronary heart disease.

For SI unit Reference Values, see

Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality.
O’Brien KD, et al: Relationship of apolipoproteins A-1 and B, and lipoprotein(a) to cardiovascular
outcomes: the AIM-HIGH trial (Atherosclerosis Intervention in Metabolic Syndrome with Low
HDL/High Triglyceride and Impact on Global Health Outcomes). J Am Coll Cardiol 2013 Oct
and the risk of vascular disease: systematic review of 40 studies involving 58,000 participants. J Am
Coll Cardiol 2010 May 11;55(19):2160-2167
**Lipoprotein Metabolism Profile**

**Clinical Information:** Lipoprotein metabolism profile analysis adds practical information about the etiology of cholesterol and/or triglyceride elevation. In some patients, increased serum lipids reflects elevated levels of intermediate-density lipoprotein (IDL), very-low-density lipoprotein (VLDL), lipoprotein a (Lp[a]), or even the abnormal lipoprotein complex-LpX. These elevations can be indicative of a genetic deficiency in lipid metabolism or transport, nephrotic syndrome, endocrine dysfunction or even cholestasis. Identification of the lipoprotein associated with lipid elevation is achieved using the gold-standard methods, which include ultracentrifugation, selective precipitation, electrophoresis, and direct measurement of cholesterol and triglycerides in isolated lipoprotein fractions. Proper characterization of a patient’s dyslipidemic phenotype aids clinical decisions and guides appropriate therapy. Classifying the hyperlipoproteinemias into phenotypes places disorders that affect plasma lipid and lipoprotein concentrations into convenient groups for evaluation and treatment. A clear distinction must be made between primary (inherited) and secondary (liver disease, alcoholism, metabolic diseases) causes of dyslipoproteinemia. Lipoprotein profiling will identify the presence of Lp(a) and LpX and distinguish between the following dyslipemias: -Exogenous hyperlipemia (Type I) -Familial Hypercholesterolemia (Type Ia) -Familial Combined Hyperlipidemia (Type IIb) -Familial dysbetalipoproteinemia (Type III) -Endogenous hyperlipemia (Type IV) -Mixed hyperlipemia (Type V)

**Useful For:** Diagnosing dyslipoproteinemia Quantitation of cholesterol and triglycerides in very-low-density lipoprotein (VLDL), LDL, HDL, and chylomicrons Identification of LpX Classifying hyperlipoproteinemias (lipoprotein phenotyping) Evaluating patients with abnormal lipid values (cholesterol, triglyceride, HDL, LDL) Quantifying lipoprotein a (Lp[a]) cholesterol

**Interpretation:** For discussion of primary disorders associated with dyslipemias see Lipids and Lipoproteins in Blood Plasma (Serum) in Special Instructions. For discussion of Lp(a), see LPAWS / Lipoprotein (a) Cholesterol, Serum.

**Reference Values:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Cholesterol (mg/dL)</strong></td>
<td>2-9 years</td>
<td>170-199 High: &gt; or =200</td>
</tr>
<tr>
<td></td>
<td>10-17 years</td>
<td>** Acceptable: high: 170-199 High: &gt; or =200</td>
</tr>
<tr>
<td></td>
<td>&gt;18 years</td>
<td>* Desirable: &lt; 200 Borderline High: 200 - 239 High: &gt; or = 240</td>
</tr>
<tr>
<td><strong>Triglycerides (mg/dL)</strong></td>
<td></td>
<td>** Acceptable: high: 75-99 High: &gt; or =100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>** Acceptable: high: 90-129 High: &gt; or =130</td>
</tr>
<tr>
<td></td>
<td></td>
<td>* Normal: high: 150-199 High: 200-499 Very high: &gt; or =500</td>
</tr>
<tr>
<td><strong>LDL Cholesterol (mg/dL)</strong></td>
<td></td>
<td>** Acceptable: high: 110-129 High: &gt; or =130</td>
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<tr>
<td><strong>LDL Triglycerides (mg/dL)</strong></td>
<td></td>
<td>&lt; or = 50</td>
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<td><strong>Apolipoprotein B (mg/dL)</strong></td>
<td></td>
<td>** Acceptable: high: 90-109 High: &gt; or =110</td>
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<tr>
<td><strong>HDL Cholesterol (mg/dL)</strong></td>
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<td>** Low: low: 40-45 Acceptable: &gt; 45</td>
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<td><strong>VLDL Cholesterol (mg/dL)</strong></td>
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<td>Undetectable</td>
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<td><strong>VLDL Triglycerides (mg/dL)</strong></td>
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<td><strong>Chylomicron Triglycerides</strong></td>
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<tr>
<td><strong>Lp(a) cholesterol</strong></td>
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<td>Undetectable</td>
</tr>
</tbody>
</table>

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  Page 1376
**Lithium, Serum**

### Clinical Information:
Lithium alters the intraneuronal metabolism of catecholamines by an unknown mechanism. It is used to suppress the manic phase of manic-depressive psychosis. Lithium is distributed throughout the total water spaces of the body and is excreted primarily by the kidney. Toxicity from lithium salts leads to ataxia, slurred speech, and confusion. Since the concentration of lithium in the serum varies with the time after the dose, blood for lithium determination should be drawn at a standard time, preferably 8 to 12 hours after the last dose (trough values).

### Useful For:
- Monitoring therapy of patients with bipolar disorders, including recurrent episodes of mania and depression
- Evaluating lithium toxicity

### Interpretation:
The therapeutic range for lithium has been established at 0.5 to 1.2 mmol/L. Within this range, most people will respond to the drug without symptoms of toxicity. However, response and side effects are individual. Lithium concentrations and side effects can increase with the loss of salt and water from the body, which can occur with a salt-free diet, excessive sweating, or an illness that causes vomiting and diarrhea. A variety of prescribed drugs, over-the-counter medications, and supplements can also increase, decrease, or interfere with the concentrations of lithium.

### Reference Values:
- Therapeutic: 0.5-1.2 mmol/L (trough concentration)
- Critical value: >1.6 mmol/L

There is no relationship between peak concentration and degree of intoxication.

### Clinical References:
**Liver Fatty Acid-Binding Protein (L-FABP) Immunostain, Technical Component Only**

**Clinical Information:** Liver fatty acid-binding protein (L-FABP) is a cytoplasmic protein that binds free fatty acids and their coenzyme A derivative, bilirubin, and other hydrophobic ligands. It may have roles in lipid transport, uptake, and metabolism. L-FABP can be used with a panel of immunohistochemical markers (beta-catenin, glutamine synthetase, C-reactive protein, and amyloid A) to distinguish hepatic adenoma from focal nodular hyperplasia and non-neoplastic liver. L-FABP is downregulated in type 1 adenomas, but is expressed in normal liver and other adenoma types.

**Useful For:** Classification of hepatic adenomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Liver Profile, Serum**

**Clinical Information:** The hepatic function panel may be used to help diagnose liver disease if a person has signs and symptoms that indicate possible liver dysfunction. If a person has a known condition or liver disease, testing may be performed at intervals to monitor the health of the liver and to evaluate the effectiveness of any treatments. Abnormal tests on a liver panel may prompt a repeat analysis of one or more tests, or of the whole panel, to see if the elevations or decreases persist and may indicate the need for additional testing to determine the cause of the liver dysfunction.

**Useful For:** Screening for liver damage, especially if someone has a condition or is taking a drug that may affect the liver

**Interpretation:** Hepatic function panel results are not diagnostic of a specific condition; they indicate that there may be a problem with the liver. In a person who does not have symptoms or identifiable risk factors, abnormal liver test results may indicate a temporary liver injury or reflect something that is happening elsewhere in the body-such as in the skeletal muscles, pancreas, or heart. It may also indicate early liver disease and the need for further testing and periodic monitoring. Results of liver panels are usually evaluated together. Several sets of results from tests performed over a few days or weeks are often assessed together to determine if a pattern is present. Each person will have a unique set of test results that will typically change over time. A healthcare practitioner evaluates the combination of liver test results to gain clues about the underlying condition. Often, further testing is necessary to determine what is causing the liver damage or disease.

**Reference Values:**
- TOTAL BILIRUBIN
  - 0-6 days: Refer to http://biltool.org/ for information on age-specific (postnatal hour of life) serum bilirubin values.
  - 7-14 days: <15.0 mg/dL
  - 15 days to 17 years: < or =1.0 mg/dL

Current as of October 11, 2018 2:20 pm CDT   800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com   Page 1378
**18 years: < or =1.2 mg/dL**

**DIRECT BILIRUBIN**
> or =12 months: 0.0-0.3 mg/dL
Reference values have not been established for patients who are under 12 months of age.

**ASPARTATE AMINOTRANSFERASE**
Males
0-11 months: not established
1-13 years: 8-60 U/L
> or =14 years: 8-48 U/L

Females
0-11 months: not established
1-13 years: 8-50 U/L
> or =14 years: 8-43 U/L

**ALANINE AMINOTRANSFERASE**
Males
> or =1 year: 7-55 U/L
Reference values have not been established for patients who are under 12 months of age.

Females
> or =1 year: 7-45 U/L
Reference values have not been established for patients who are under 12 months of age.

**ALKALINE PHOSPHATASE**
Males
4 years: 149-369 U/L
5 years: 179-416 U/L
6 years: 179-417 U/L
7 years: 172-405 U/L
8 years: 169-401 U/L
9 years: 175-411 U/L
10 years: 191-435 U/L
11 years: 185-507 U/L
12 years: 185-562 U/L
13 years: 182-587 U/L
14 years: 166-571 U/L
15 years: 138-511 U/L
16 years: 102-417 U/L
17 years: 69-311 U/L
18 years: 52-222 U/L
> or =19 years: 45-115 U/L

Females
4 years: 169-372 U/L
5 years: 162-355 U/L
6 years: 169-370 U/L
7 years: 183-402 U/L
8 years: 199-440 U/L
9 years: 212-468 U/L
10 years: 215-476 U/L
11 years: 178-526 U/L
12 years: 133-485 U/L
13 years: 120-449 U/L
14 years: 153-362 U/L
15 years: 75-274 U/L
16 years: 61-264 U/L
17-23 years: 52-144 U/L
24-45 years: 37-98 U/L
46-50 years: 39-100 U/L
51-55 years: 41-108 U/L
56-60 years: 46-118 U/L
61-65 years: 50-130 U/L
> or =66 years: 55-142 U/L
Reference values have not been established for patients who are under 4 years of age.

ALBUMIN
> or =12 months: 3.5-5.0 g/dL
Reference values have not been established for patients who are under 12 months of age.

TOTAL PROTEIN
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients who are under 12 months of age.


Liver/Kidney Microsome Type 1 Antibodies, Serum

Clinical Information: Autoimmune liver disease (eg, autoimmune hepatitis and primary biliary cirrhosis) is characterized by the presence of autoantibodies including smooth muscle antibodies (SMA), antimitochondrial antibodies (AMA), and anti-liver/kidney microsomal antibodies type 1 (anti-LKM-1).(1) Subtypes of autoimmune hepatitis (AIH) are based on autoantibody reactivity patterns. Anti-LKM-1 antibodies serve as a serologic marker for AIH type 2 and typically occur in the absence of SMA and antinuclear antibodies. These antibodies react with a short linear sequence of the recombinant antigen cytochrome monoxygenase P450 2D6.(2) Patients with AIH type 2 more often tend to be young, female, and have severe disease that responds well to immunosuppressive therapy.

Useful For: Evaluation of patients with liver disease of unknown etiology Evaluation of patients with suspected autoimmune hepatitis

Interpretation: Seropositivity for anti-LKM-1 antibodies is consistent with a diagnosis of AIH type 2.

Reference Values:
< or =20.0 Units (negative)
20.1-24.9 Units (equivocal)
> or =25.0 Units (positive)
Reference values apply to all ages.


Lobster, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in
infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;0.35</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


**Locust Black (Robinia pseudoacacia) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 < 0.69 Low Positive 2 0.70 < 3.49 Moderate Positive 3 3.50 < 17.49 Positive 4 17.50 < 49.99 Strong Positive 5 50.00 < 99.99 Very Strong Positive 6 >= 99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

**Long QT Syndrome Multi-Gene Panel, Blood**

**Clinical Information:** Long QT syndrome (LQTS) is a genetic cardiac disorder characterized by QT prolongation and T-wave abnormalities on electrocardiogram (EKG), which may result in recurrent syncope, ventricular arrhythmia, and sudden cardiac death. Romano-Ward syndrome (RWS), which accounts for the majority of LQTS, follows an autosomal dominant inheritance pattern and is caused by pathogenic variants in genes that encode cardiac ion channels or associated proteins. The diagnosis of RWS is established by the prolongation of the QTc interval in the absence of other conditions or factors that may lengthen it, such as QT-prolonging drugs or structural heart abnormalities. Clinical factors such as a history of syncope and family history also contribute to the diagnosis of RWS. RWS has an estimated prevalence of 1 in 3,000 individuals. Of the families who meet clinical diagnostic criteria for RWS, approximately 75% have known genetic causes, while approximately 25% have no detectable pathogenic variants in any of the genes known to cause RWS. Approximately 3% of RWS cases are the...
result of large deletions or duplications in KCNQ1 or KCNH2. Deletions/duplications have not been reported in the other genes implicated in RWS. Only about half of the individuals with a pathogenic gene variant associated with RWS have symptoms, usually one to a few syncopal spells, and thus many patients with this condition unfortunately present with sudden cardiac death as their first symptom. Cardiac events may occur any time from infancy through adulthood, but are most common from the preteen years through the 20s. Additionally, RWS is believed to account for approximately 10% to 15% of sudden infant death syndrome (SIDS) cases. In some cases, LQTS may be associated with congenital profound bilateral sensorineural hearing loss, known as Jervell and Lange-Nielsen syndrome (JLNS). JLNS is inherited in an autosomal recessive inheritance pattern and is caused by homozygous or compound heterozygous pathogenic variants in either KCNQ1 or KCNE1. Timothy syndrome (TS) is a multisystem disorder involving prolonged QT interval in association with congenital anomalies that may include hand/foot syndactyly, structural heart defects, facial dysmorphology, and neurodevelopmental features. Ventricular tachyarrhythmia is the leading cause of death with an average age of death of 2.5 years. TS is inherited in an autosomal dominant manner and usually occurs as a result of a de novo heterozygous variant in the CACNA1C gene. Management strategies for LQTS include pharmacologic therapies, implantable cardioverter defibrillators (ICD), or other surgical interventions, and lifestyle restrictions such as avoidance of competitive sports or other triggers for cardiac events. In some cases, knowledge of the LQTS genotype may assist in tailoring an individual's treatment plan. For example, patients with an SCN5A pathogenic variant may not respond well to the typical first-line therapy of beta-blockers and may have a lower threshold for consideration of an ICD. Genetic testing in LQTS is recommended and supported by multiple consensus statements to confirm the clinical diagnosis, assist with risk stratification, guide management, and identify at-risk family members. Even individuals with a normal QT interval may still be at risk for a cardiac event and sudden cardiac death and, thus, EKG analysis alone is insufficient to rule out the diagnosis and genetic testing is necessary to confirm the presence or absence of disease in at-risk family members. Pre- and posttest genetic counseling is an important factor in the diagnosis and management of LQTS and is supported by expert consensus statements.

**Useful For:**
Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of long QT syndrome (LQTS) Establishing a diagnosis of a LQTS, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying variants within genes known to be associated with increased risk for disease features and allowing for predictive testing of at-risk family members

**Interpretation:**
Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Lorazepam (Ativan), Serum

Reference Values:
Reference Range: 50.0 - 240.0 ng/mL

Low-Grade Fibromyxoid Sarcoma (LGFMS), 16p11.2 (FUS or TLS) Rearrangement, FISH, Tissue

Clinical Information: Low-grade fibromyxoid sarcoma (LGFMS) is a rare malignant soft tissue tumor characterized by a bland fibroblastic spindle cell proliferation arranged in alternating fibrous and myxoid areas, with or without giant collagen rosettes. These tumors are characterized by the chromosome translocation t(7;16)(q33-34;p11), which results in the fusion of FUS (also called TLS) on chromosome 16 to CREB3L2 (also called BBF2H7) on chromosome 7. Greater than 70% of LGFMS are cytogenetically characterized by this translocation. In rare cases, a variant t(11;16)(p11;p11) has been described in which FUS is fused to CREB3L1 (OASIS), a gene structurally related to CREB3L2. Testing of FUS locus rearrangement should be concomitant with histologic evaluation, and positive results may support the diagnosis of LGFMS.

Useful For: Supporting the diagnosis of low-grade fibromyxoid sarcoma when used in conjunction with an anatomic pathology consultation

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the FUS probe set. A positive result is consistent with the diagnosis of low-grade fibromyxoid sarcoma (LGFMS). A negative result suggests that a FUS gene rearrangement is not present, but does not exclude the diagnosis of LGFMS.

Reference Values:
An interpretative report will be provided.

Clinical References:
1. Fletcher CDM, Unni K, Mertens F: World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Soft Tissue and Bone. IARC: Lyon 2002, pp 104-105

Loxapine (Loxitaner) and 8-Hydroxyloxapine

Reference Values:
Loxapine:
Clinical Information: Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the FDA for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Next-generation sequencing has recently emerged as an accurate, cost-effective method to identify alterations across numerous genes known to be associated with response or resistance to specific targeted therapies. This test uses formalin-fixed paraffin-embedded tissue or cytology slides to assess for common rearrangements (fusions) involving 4 genes known to be associated with lung cancer. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with lung tumors. These data can also be used to help determine clinical trial eligibility for patients with alterations in genes not amenable to current FDA-approved targeted therapies. See Activated/Partner Gene Breakpoints Resulting in Targeted Fusion Transcripts Interrogated by Lung Panel in Special Instructions for details regarding the targeted gene regions evaluated by this test.

Useful For: Identifying lung tumors that may respond to targeted therapies by simultaneously assessing multiple genes involved in rearrangements resulting in fusion transcripts Diagnosis and management of patients with lung cancer

Interpretation: An interpretive report will be provided.

Clinical References:
The drug Xalkori works by blocking certain kinases, including those produced by the abnormal ALK gene. Clinical studies have demonstrated that Xalkori treatment of patients with tumors exhibiting ALK rearrangements can halt tumor progression or result in tumor regression.

**Useful For:** Identifying patients with late-stage, non-small cell lung cancers who may benefit from treatment with the drug Xalkori

**Interpretation:** A positive result (ALK rearrangement identified) is detected when the percent of cells with an abnormality exceeds the normal cutoff for the ALK probe set. A positive result suggests rearrangement of the ALK locus and a tumor that may be responsive to ALK inhibitor therapy. A negative result suggests no rearrangement of the ALK gene region at 2p23. A specimen is considered positive if >50% demonstrate a signal pattern consistent with an ALK rearrangement and considered negative if <10% of cells are positive. If the results are equivocal (>10% and <50%), an additional 50 cells are scored and would be considered positive if >15% of cells exhibit a signal pattern consistent with an ALK rearrangement and negative if <15% of cells exhibit an ALK rearrangement.

**Reference Values:**
An interpretative report will be provided.


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**Lung Cancer, EGFR with ALK Reflex, Tumor**

**Clinical Information:** Lung cancer is the leading cause of cancer death in the United States. Non-small cell lung carcinoma (NSCLC) accounts for 75% to 80% of all lung cancers with an overall 5-year survival rate of 10% to 15%. Standard chemotherapy regimens have had marginal success in improving clinical outcomes. Epidermal growth factor receptor (EGFR) is activated by the binding of specific ligands, resulting in activation of the RAS/MAPK pathway. EGFR-targeted therapies (eg, gefitinib and erlotinib) have been approved by the FDA for use in treating patients with NSCLC who previously failed to respond to traditional chemotherapy. EGFR tyrosine kinase inhibitors have also been shown to increase progression-free and overall survival in patients who receive these therapies as a first-line therapy for the treatment of NSCLC. Agents such as gefitinib and erlotinib, which prevent ATP binding to EGFR kinase, do not appear to have any meaningful inhibitor activity on tumors that lack an activating EGFR mutation or in tumors that demonstrate the presence of drug-resistant EGFR mutations (eg, exon 20 insertions and T790M). Therefore, current data suggest that the efficacy of EGFR-targeted therapies in NSCLC is confined to patients with tumors demonstrating the presence of EGFR-activating mutations such as L858R, L861Q, G719A/S/C, S768I, or small deletions within exon 19 and the absence of drug-resistant mutations. As a result, the mutation status of EGFR is a critical marker for selecting patients for EGFR-targeted therapy. Rearrangements of the anaplastic lymphoma kinase (ALK) locus are found in a subset of lung carcinomas (generally EGFR wild-type tumors) and their identification by FISH may guide important therapeutic decisions for the management of these tumors. The fusion of the EML4 (echinoderm microtubule-associated protein-like 4) gene with the ALK (anaplastic large cell lymphoma kinase) gene results from an inversion of chromosome band 2p23. The ALK-EML4 rearrangement has been identified in 3% to 5% of NSCLC with the majority occurring in adenocarcinoma and younger male patients who were light or nonsmokers. Recent studies have demonstrated that lung cancers harboring ALK rearrangements are resistant to epidermal growth factor receptor tyrosine kinase inhibitors, but may be highly sensitive to ALK inhibitors, like crizotinib (Xalkori). The drug crizotinib works by blocking certain kinases, including those produced by the abnormal ALK gene. Clinical studies have demonstrated that crizotinib treatment of patients with
tumors exhibiting ALK rearrangements can halt tumor progression or result in tumor regression. The ALK/EML4 FISH assay is an FDA-approved companion diagnostic test for crizotinib, which was recently approved by the FDA to treat certain patients with late-stage (locally advanced or metastatic), non-small cell lung cancers that harbor ALK gene rearrangements. It is useful for the identification of lung cancer patients who will benefit from crizotinib therapy.

**Useful For:** Identifying non-small cell lung cancers that may benefit from treatment with epidermal growth factor receptor-tyrosine kinase or anaplastic lymphoma kinase inhibitors

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Lung Cancer, RET (10q11) Rearrangement, FISH, Tissue**

**Clinical Information:** Lung cancer is the leading cause of cancer mortality in developed countries. The discovery of a variety of genetic alterations in non-small-cell lung cancer (NSCLC) has enabled the use of targeted therapy such as the anaplastic lymphoma kinase (ALK) inhibitor, crizotinib, and the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, erlotinib, for NSCLC with ALK rearrangements and EGFR mutations, respectively. Abnormalities of the RET proto-oncogene at chromosome 10q11 have been identified as the causative genetic abnormality in the neoplasia predisposition syndrome multiple endocrine neoplasia type II (MEN2), as well as in thyroid carcinomas. Recently, chromosomal rearrangements of RET have been identified in a subset of lung adenocarcinomas. Patients with tumors harboring RET rearrangements may benefit from RET kinase inhibitors, but the clinical benefits of the inhibitor has not yet been clarified.

**Useful For:** Identifying RET gene rearrangements in patients with late-stage, lung adenocarcinomas that are negative for EGFR mutations and ALK rearrangements

**Interpretation:** A positive result is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result suggests rearrangement of the RET locus and a tumor that may be responsive to RET kinase inhibitor therapy. A negative result suggests no rearrangement of the RET gene region at 10q11.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Lung Cancer, ROS1 (6q22) Rearrangement, FISH, Tissue**

**Clinical Information:** The discovery of a variety of genetic alterations in non-small-cell lung cancer (NSCLC) has enabled the use of targeted therapy such as the anaplastic lymphoma kinase (ALK) inhibitor, crizotinib, and the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, erlotinib, for NSCLC with ALK rearrangements and EGFR mutations, respectively. Abnormalities of the RET proto-oncogene at chromosome 10q11 have been identified as the causative genetic abnormality in the neoplasia predisposition syndrome multiple endocrine neoplasia type II (MEN2), as well as in thyroid carcinomas. Recently, chromosomal rearrangements of RET have been identified in a subset of lung adenocarcinomas. Patients with tumors harboring RET rearrangements may benefit from RET kinase inhibitors, but the clinical benefits of the inhibitor has not yet been clarified.

**Useful For:** Identifying RET gene rearrangements in patients with late-stage, lung adenocarcinomas that are negative for EGFR mutations and ALK rearrangements

**Interpretation:** A positive result is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result suggests rearrangement of the RET locus and a tumor that may be responsive to RET kinase inhibitor therapy. A negative result suggests no rearrangement of the RET gene region at 10q11.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
**Clinical Information:** Lung cancer is the leading cause of cancer mortality in developed countries. The discovery of a variety of genetic alterations in non-small-cell lung cancer (NSCLC) has enabled the use of targeted therapy such as the anaplastic lymphoma kinase (ALK) inhibitor, crizotinib, and the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, erlotinib, for NSCLC with ALK rearrangements and EGFR mutations, respectively. The c-ros oncogene 1 (ROS1), originally described in glioblastomas, has been identified as a potential relevant therapeutic target in lung adenocarcinoma. Crizotinib has shown in vitro activity and early evidence of clinical activity in ROS1-rearranged tumors.

**Useful For:** Identifying c-ros oncogene 1 (ROS1) gene rearrangements in patients with late-stage, lung adenocarcinomas that are negative for epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result suggests rearrangement of the ROS1 locus and a tumor that may be responsive to ALK-inhibitor therapy. A positive result suggests rearrangement of the c-ros oncogene 1 (ROS1) locus and a tumor that may be responsive to anaplastic lymphoma kinase (ALK)-inhibitor therapy

**Reference Values:**
An interpretive report will be provided.


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**Lung Cancer-Targeted Gene Panel with Rearrangement, Tumor**

**Clinical Information:** Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the FDA for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Next-generation sequencing has recently emerged as an accurate, cost-effective method to identify alterations across numerous genes known to be associated with response or resistance to specific targeted therapies. This is a single assay that uses formalin-fixed paraffin-embedded tissue or cytology slides to assess for common somatic mutations and rearrangements (fusions) involving 11 genes known to be associated with lung cancer. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with lung tumors. These data can also be used to help determine clinical trial eligibility for patients with alterations in genes not amenable to current FDA-approved targeted therapies. See Targeted Gene Regions Interrogated by Lung Panel and Activated/Partner Gene Breakpoints Resulting in Targeted Fusion Transcripts Interrogated by Lung Panel in Special Instructions for details regarding the targeted gene regions evaluated by this test.

**Useful For:** Identifying lung tumors that may respond to targeted therapies by assessing multiple gene targets simultaneously in EGFR, BRAF, KRAS, HRAS, NRAS, ALK, ERBB2, MET, ALK, ROS1, RET, and NTRK1 genes Diagnosis and management of patients with lung cancer

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:** 1. Beadling C, Neff TL, Heinrich MC, et al: Combining highly multiplexed

LUNGP

Lung Cancer-Targeted Gene Panel, Tumor

Clinical Information: Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the FDA for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Next-generation sequencing has recently emerged as an accurate, cost-effective method to identify alterations across numerous genes known to be associated with response or resistance to specific targeted therapies. This test uses formalin-fixed paraffin-embedded tissue or cytology slides to assess for common somatic mutations in 8 genes known to be associated with lung cancer. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with lung tumors. These data can also be used to help determine clinical trial eligibility for patients with alterations in genes not amenable to current FDA-approved targeted therapies. See Targeted Gene Regions Interrogated by Lung Panel in Special Instructions for details regarding the targeted gene regions evaluated by this test.

Useful For: Identifying lung tumors that may respond to targeted therapies by assessing multiple gene targets within the EGFR, BRAF, KRAS, HRAS, NRAS, ALK, ERBB2, and MET genes simultaneously

Diagnosis and management of patients with lung cancer

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretative report will be provided.

**LUPN**

**Lupin, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
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<tr>
<td>0</td>
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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


---

**FLUPV**

**Lupus Anticoagulant Evaluation with Reflex**

**Reference Values:**

Lupus Anticoagulant: Not Detected

This interpretation is based on the following test results:

- **PTT-LA Screen**: < or = 40 seconds
- **DRVVT Screen**: < or = 45 seconds
**Lupus Anticoagulant Profile**

**Clinical Information:** Lupus anticoagulant (LAC) is an antibody to negatively charged phospholipid that interferes with phospholipid-dependent coagulation tests. LAC is found in, but not limited to, patients with systemic lupus erythematosus; LAC is associated with other autoimmune disorders and collagen vascular disease, and occurs in response to medications or certain infections (e.g., respiratory tract infections in children) and in individuals with no obvious underlying disease. LAC has been associated with arterial and venous thrombosis and fetal loss. Individuals with thrombocytopenia or factor II deficiency associated with LAC may be at risk for bleeding.

**Useful For:** Confirming or excluding the presence of lupus anticoagulant (LAC), distinguishing LAC from specific coagulation factor inhibitors and nonspecific inhibitors, investigating a prolonged activated thromboplastin time, especially when combined with other coagulation studies.

**Interpretation:** An interpretive report will be provided when testing is complete.

**Reference Values:**

- **PROTHROMBIN TIME (PT)**
  - 10.3-12.8 seconds

- **INR**
  - 0.9-1.2

  The INR is used only for patients on stable oral anticoagulant therapy. It makes no significant contribution to the diagnosis or treatment of patients whose PT is prolonged for other reasons.

- **ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT)**
  - Adults: 26-36 seconds
    - The normal full-term newborn APTT may be up to 35% longer than in adults and even longer (up to twice the adult upper limit) in healthy premature infants. Typically, the APTT is in the adult reference range by age 3 months in healthy full-term infants and by age 6 months in healthy premature infants (30-60 weeks gestation) *.
    - 26-36 seconds (>3-6 months)
  - 26-36 seconds (>3-6 months)
  - *See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

- **DILUTE RUSSELL'S VIPER VENOM TIME**
  - <1.2

**Clinical References:**


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**Luteinizing Hormone (LH) Beta Immunostain, Technical Component Only**

**Clinical Information:** In males, luteinizing hormone (LH) stimulates androgen production by Leydig cells in the testes. In females, LH stimulates androgen and progesterone synthesis in ovarian follicles and corpus luteum, and promotes ovulation. A sparse population of cells (approximately 10%) stain positively in normal pituitary gland. This population of gonadotrophs also produces follicle-stimulating hormone. Immunohistochemical detection of LH beta may be useful in the classification of pituitary adenomas.

**Useful For:** Classification of pituitary adenomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a
pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.


**Luteinizing Hormone (LH), Pediatrics, Serum**

**Clinical Information:** Luteinizing hormone (LH) is a glycoprotein hormone consisting of 2 noncovalently bound subunits (alpha and beta). LH is produced by the anterior pituitary gland under regulation of the hypothalamic gonadotropin releasing hormone (GnRH) and feedback from gonadal steroid hormones. In children, LH, along with follicle-stimulating hormone (FSH), is used to diagnose precocious (early) and delayed puberty. Precocious puberty refers to the appearance of physical and hormonal signs of pubertal development at an earlier age than is considered normal (before 8 years in girls and 9 years in boys). Evaluation of precocious puberty includes measurement of LH and FSH to determine whether gonadotropins are increased in relation to chronologic age (gonadotropin-dependent) or whether sex steroid secretion is occurring independent of LH and FSH (gonadotropin-independent). In gonadotropin-dependent precocious puberty, basal LH levels are often elevated into the pubertal range and show a pubertal (heightened) response to GnRH stimulation. In gonadotropin-independent precocious puberty, the LH level is low at baseline and fails to respond to GnRH stimulation. Delayed puberty is defined clinically by the absence or incomplete development of secondary sexual characteristics by 14 years in boys and by 12 years in girls. Delayed puberty usually results from inadequate gonadal steroid secretion that, in turn, is most often caused by a defective gonadotropin secretion from the anterior pituitary, due to defective production of GnRH from the hypothalamus. Random measurements of LH and FSH, together with estradiol (females) or testosterone (males), are useful to distinguish between primary and secondary causes of delayed puberty.

**Useful For:** Diagnosis of precocious puberty and delayed puberty in children

**Interpretation:** In young children, high levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), along with the development of secondary sexual characteristics at an unusually young age, are an indication of gonadotropin-dependent precocious puberty (also called central precocious puberty). Prepubertal levels of LH and FSH in children exhibiting some signs of pubertal changes may be an indication of gonadotropin-independent precocious puberty (also refer as precocious pseudopuberty). In precocious pseudopuberty the signs and symptoms are the result of elevated levels of estrogen in girls or testosterone in boys. In delayed puberty, LH and FSH levels can be normal or below what is expected for a youth within this age range. The test for LH response to gonadotropin releasing hormone in addition to other testing may help to diagnose the reason for the delayed puberty.

**Reference Values:**

Females

- <1 year: <0.02-18.3 IU/L
- 1-8 years: <0.02-0.3 IU/L
- 9-10 years: <0.02-4.8 IU/L
- 11-13 years: <0.02-11.7 IU/L
- 14-17 years: <0.02-16.7 IU/L
Tanner Stages
Stage I (1-8 years): <0.02-0.3 IU/L
Stage II: <0.02-4.1 IU/L
Stage III: 0.6-7.2 IU/L
Stage IV-V: 0.9-13.3 IU/L

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/- 2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African-American girls. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.

Males
<1 year: <0.02-5.0 IU/L
1-8 years: <0.02-0.5 IU/L
9-10 years: <0.02-3.6 IU/L
11-13 years: 0.1-5.7 IU/L
14-17 years: 0.8-8.7 IU/L

Tanner Stages
Stage I (1-8 years): <0.02-0.5 IU/L
Stage II: 0.03-3.7 IU/L
Stage III: 0.09-4.2 IU/L
Stage IV-V: 1.3-9.8 IU/L

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/- 2) years. For boys there is no proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (adult) should be reached by age 18.


Luteinizing Hormone (LH), Serum

Clinical Information: Luteinizing hormone (LH) is a glycoprotein hormone consisting of 2 noncovalently bound subunits (alpha and beta). The alpha subunit of LH, follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and human chorionic gonadotropin (hCG) are identical and contain 92 amino acids. The beta subunits of these hormones vary and confer the hormones' specificity. LH has a beta subunit of 121 amino acids and is responsible for interaction with the LH receptor. This beta subunit contains the same amino acids in sequence as the beta subunit of hCG and both stimulate the same receptor, however, the hCG-beta subunit contains an additional 24 amino acids, and the hormones differ in the composition of their sugar moieties. Gonadotropin-releasing hormone from the hypothalamus controls the secretion of the gonadotropins, FSH, and LH, from the anterior pituitary. In both males and females, LH is essential for reproduction. In females, the menstrual cycle is divided by a midcycle surge of both LH and FSH into a follicular phase and a luteal phase. This "LH surge" triggers ovulation thereby not only releasing the egg, but also initiating the conversion of the residual follicle into a corpus luteum that, in turn, produces progesterone to prepare the endometrium for a possible implantation. LH is necessary to maintain luteal function for the first 2 weeks. In case of pregnancy, luteal function will be further maintained by the action of hCG (a hormone very similar to LH) from the newly established pregnancy. LH supports thecal cells in the ovary that provide androgens and hormonal precursors for estradiol production. LH in males acts on testicular interstitial cells of Leydig to cause increased synthesis of testosterone.

Useful For: An adjunct in the evaluation of menstrual irregularities Evaluating patients with suspected hypogonadism Predicting ovulation Evaluating infertility Diagnosing pituitary disorders

Interpretation: In both males and females, primary hypogonadism results in an elevation of basal
follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. Postmenopausal LH levels are generally above 40 IU/L. (Note: FSH / Follicle-Stimulating Hormone (FSH), Serum is the preferred test to confirm menopausal status) FSH and LH are generally elevated in: - Primary gonadal failure - Complete testicular feminization syndrome - Precocious puberty (either idiopathic or secondary to a central nervous system lesion) - Menopause - Primary ovarian hypofunction in females - Polycystic ovary disease in females - Primary hypogonadism in males LH is decreased in: - Primary ovarian hyperfunction in females - Primary hypergonadism in males FSH and LH are both decreased in failure of the pituitary or hypothalamus.

**Reference Values:**

**Males**

< or =4 weeks: Not established  
>1 month-< or =12 months: < or =0.4 IU/L  
>12 months-< or =6 years: < or =1.3 IU/L  
>6-< or =11 years: < or =1.4 IU/L  
>11-< or =14 years: 0.1-7.8 IU/L  
>14-< or =18 years: 1.3-9.8 IU/L  
>18 years: 1.3-9.6 IU/L

**Females**

< or =4 weeks: Not established  
>1-< or =12 months: < or =0.4 IU/L  
>12 months-< or =6 years: < or =0.5 IU/L  
>6-< or =11 years: < or =3.1 IU/L  
>11-< or =14 years: < or =11.9 IU/L  
>14-< or =18 years: 0.5-41.7 IU/L

Premenopausal:  
Follicular: 1.9-14.6 IU/L  
Midcycle: 12.2-118.0 IU/L  
Luteal: 0.7-12.9 IU/L  
Postmenopausal: 5.3-65.4 IU/L


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**Lyme Central Nervous System Infection IgG with Antibody Index Reflex, Serum and Spinal Fluid**

**Clinical Information:** Lyme disease is a multisystem and multistage tick-transmitted infection caused by spirochetal bacteria in the Borrelia burgdorferi sensu lato (Bbsl) complex. Nearly all human infections are caused by 3 Bbsl species; B burgdorferi sensu stricto (hereafter referred to as B burgdorferi) is the primary cause of Lyme disease in North America, while B afzelii and B garinii are the primary causes of Lyme disease in Europe and parts of Asia. Lyme disease is the most commonly reported tick-borne infection in North America and Europe, causing an estimated 300,000 cases in the United States each year and 85,000 cases in Europe. The clinical features of Lyme disease are broad and may be confused with various immune and inflammatory disorders. The classic presenting sign of early localized Lyme disease caused by B burgdorferi is erythema migrans (EM), which occurs in approximately 80% of individuals. Other early signs and symptoms include malaise, headache, fever, lymphadenopathy, and myalgia. Arthritis, cardiac disease, and neurological disease may be later stage manifestations. Neuroinvasive Lyme disease (NLD) can affect either the peripheral or central nervous system, with patients classically presenting with the triad of lymphocytic meningitis, cranial neuropathy (especially facial nerve palsy) and radiculoneuritis, which can affect the motor or sensory nerves, or both. These symptoms can occur in any combination or alone. Some patients may present with Bannwarth syndrome, which includes painful radiculoneuritis with variable motor weakness. NLD
should be considered in individuals presenting with appropriate symptoms who have had exposure to ticks in a Lyme endemic region of the United States, Europe or Asia. Patients meeting these criteria should be evaluated for the presence of anti-Bbsl antibodies in serum using the standard 2-tiered testing algorithm (LYME / Lyme Disease Serology, Serum) as recommended by the CDC. Briefly, the LYME test includes testing of serum specimens by an anti-Bbsl antibody ELISA, followed by supplemental testing of all reactive samples using an immunoblot or western blot for detection of IgM- and IgG-class antibodies to Bbsl. Notably, the majority of patients with NLD, will be seropositive in serum. Therefore, it is recommended that all patients tested by this assay, also have LYME / Lyme Disease Serology, Serum performed. Results from these assays, alongside appropriate exposure history and clinical presentation, may be used to establish a diagnosis of NLD. Spinal fluid (CSF) may also be tested for the presence of antibodies to Bbsl using the current 2-tiered testing algorithm as defined for serum samples. However, there are currently no interpretive criteria for assessment of anti-Bbsl IgM and IgG immunoblot banding patterns in CSF. Additionally, while the presence of antibodies to Bbsl in CSF may be due to true intrathecal antibody synthesis, thus indicating CNS infection, antibodies may alternatively be present as a result of passive diffusion through the blood-brain barrier or due to blood contamination of CSF during a traumatic lumbar puncture. The Lyme CNS infection antibody index is performed as a reflex and quantitatively measures the level of anti-Bbsl antibodies in CSF and serum, ideally collected within 24 hours of each other, and normalizes those levels to total IgG and albumin in both specimen sources. A positive Lyme CNS AI indicates true intrathecal antibody synthesis of antibodies to Bbsl, which alongside clinical and exposure history can be used to establish a diagnosis of NLD.

**Useful For:** Aiding in the diagnosis of neuroinvasive Lyme disease or neuroborreliosis due to Borrelia species associated with Lyme disease (eg, B burgdorferi, B garinii, B afzelli)

**Interpretation:** Negative: No antibodies to Lyme disease causing Borrelia species detected in spinal fluid. A negative result in a patient with appropriate exposure history and symptoms consistent with neuroinvasive Lyme disease should not be used to exclude infection. Testing for antibodies to Lyme disease-causing Borrelia species in serum should be performed. Reactive: Supplemental testing to determine a Lyme central nervous system antibody index has been ordered. Diagnosis of neuroinvasive Lyme disease should not be established solely based on a reactive screening result.

**Reference Values:**
Negative


**LNBAI**

**Lyme CNS Infection IgG, Antibody Index**

**Clinical Information:** Lyme disease is a multisystem and multistage tick-transmitted infection caused by spirochetal bacteria in the Borrelia burgdorferi sensu lato (Bbsl) complex. Nearly all human infections are caused by 3 Bbsl species; B burgdorferi sensu stricto (hereafter referred to as B burgdorferi) is the primary cause of Lyme disease in North America, while B afzelii and B garinii are the primary causes of Lyme disease in Europe and parts of Asia. Lyme disease is the most commonly reported tick-borne infection in North America and Europe, causing an estimated 300,000 cases in the United States each year and 85,000 cases in Europe. The clinical features of Lyme disease are broad and may be confused with various immune and inflammatory disorders. The classic presenting sign of early localized Lyme disease caused by B burgdorferi is erythema migrans (EM), which occurs in approximately 80% of individuals. Other early signs and symptoms include malaise, headache, fever, lymphadenopathy, and myalgia. Arthritis, cardiac disease, and neurological disease may be later stage manifestations. Neuroinvasive Lyme disease (NLD) can affect either the peripheral or central nervous system, with patients classically...
presenting with the triad of lymphocytic meningitis, cranial neuropathy (especially facial nerve palsy) and radiculoneuritis, which can affect the motor or sensory nerves, or both. These symptoms can occur in any combination or alone. Some patients may present with Bannwarth syndrome, which includes painful radiculoneuritis with variable motor weakness. NLD should be considered in individuals presenting with appropriate symptoms who have had exposure to ticks in a Lyme endemic region of the United States, Europe or Asia. Patients meeting these criteria should be evaluated for the presence of anti-Bbsl antibodies in serum using the standard 2-tiered testing algorithm as recommended by the Centers for Disease Control and Prevention (CDC). Briefly, the STTTA includes testing of serum specimens by an anti-Bbsl antibody ELISA, followed by supplemental testing of all reactive samples using an immunoblot or western blot for detection of IgM- and IgG- class antibodies to Bbsl. Notably, the majority of patients with NLD, more than 99%, will be seropositive in serum. This alongside appropriate exposure history and clinical presentation may be used to establish a diagnosis of NLD. Cerebrospinal fluid (CSF) may also be tested for the presence of antibodies to Bbsl using the current 2-tiered testing algorithm as defined for serum samples. However, there are currently no interpretive criteria for assessment of anti-Bbsl IgM and IgG immunoblot banding patterns in CSF. Additionally, while the presence of antibodies to Bbsl in CSF may be due to true intrathecal antibody synthesis, thus indicating CNS infection, antibodies may alternatively be present as a result of passive diffusion through the blood-brain barrier or due to blood contamination of CSF during a traumatic lumbar puncture. The Lyme CNS Antibody Index (AI) quantitatively measures the level of anti-Bbsl antibodies in CSF and serum, ideally collected within 24 hours of each other, and normalizes those levels to total IgG and albumin in both specimen sources. A positive Lyme CNS AI indicates true intrathecal antibody synthesis of antibodies to Bbsl, which alongside clinical and exposure history can be used to establish a diagnosis of NLD.

Useful For: Aids in the diagnosis of neuroinvasive Lyme disease or neuroborreliosis due to Borrelia species associated with Lyme disease (eg, B burgdorferi, B garinii, B afzelli)

Interpretation: Negative (Lyme CNS AI 0.6 to <1.3): Results indicate lack of intrathecal antibody synthesis to Lyme disease associated Borrelia species. This suggests the absence of neuroinvasive Lyme disease. The initial screen reactive result may be due to anti-Borrelia species antibodies present in the CSF due to increased permeability of the blood-brain barrier or transient introduction during lumbar puncture. Equivocal (Lyme CNS AI 1.3 to 1.5): Low level of intrathecal antibody synthesis to Lyme disease associated Borrelia species detected. Results should be correlated with exposure history and clinical presentation to establish a diagnosis of neuroinvasive Lyme disease. Positive (Lyme CNS AI >1.5): Results indicate the presence of intrathecal antibody synthesis to Lyme disease associated Borrelia species, suggesting neuroinvasive Lyme disease. Results should be correlated with exposure history and clinical presentation to establish the diagnosis. Invalid (Lyme CNS AI <0.6): Result is due to abnormally elevated total IgG levels in CSF. This may be due to passive diffusion through the blood-brain barrier or contamination of the cerebrospinal fluid with blood during a traumatic lumbar puncture. Repeat testing may be considered.

Reference Values:
Only orderable as a reflex. For more information see LNBAB / Lyme CNS Infection IgG with Antibody Index Reflex.


LYWB 9535 Lyme Disease Antibody, Immunoblot, Serum

Clinical Information: Lyme disease is caused by the spirochete Borrelia burgdorferi. The spirochete is transmitted to humans through the bite of Ixodes species ticks. Endemic areas for Lyme disease in the United States (US) correspond with the distribution of 2 tick species, Ixodes dammini (Northeastern and upper Midwestern US) and Ixodes pacificus (West Coast US). In Europe, Ixodes ricinus transmits the spirochete. Lyme disease exhibits a variety of symptoms that may be confused with immune and inflammatory disorders. Inflammation around the tick bite causes skin lesions. Erythema chronicum migrans (ECM), a unique expanding skin lesion with central clearing that results in a ring-like appearance, is the first stage of the disease. Any of the following clinical manifestations may...
be present in patients with Lyme disease: arthritis, neurological or cardiac disease, or skin lesions. Neurologic and cardiac symptoms may appear with stage 2 and arthritic symptoms with stage 3 of Lyme disease. In some cases, a definitive distinction between stages is not always seen. Further, secondary symptoms may occur even though the patient does not recall having a tick bite or a rash. The Second National Conference on the Serologic Diagnosis of Lyme Disease (1994) recommended that laboratories use a 2-test approach for the serologic diagnosis of Lyme disease. Accordingly, specimens are first tested by the more sensitive EIA. An immunoblot assay is used to supplement positive or equivocal Lyme (EIA). An immunoblot identifies the specific proteins to which the patient’s antibodies bind. Although there are no proteins that specifically diagnose B burgdorferi infection, the number of proteins recognized in the immunoblot assay is correlated with diagnosis. Culture or PCR of skin biopsies obtained near the margins of ECM are frequently positive. In late (chronic) stages of the disease, serology is often positive and the diagnostic method of choice. PCR testing also may be of use in these late stages if performed on synovial fluid or cerebrospinal fluid. Diagnosis of neuroinvasive Lyme disease (ie, neuroborreliosis) can be achieved by determining the Lyme antibody index value using paired serum and cerebrospinal fluid samples (LNBAB / Lyme CNS Infection IgG with Antibody Index Reflex).

**Useful For:** Aids in the diagnosis of systemic Lyme disease

**Interpretation:** IgM: IgM antibodies to Borrelia burgdorferi may be detectable within 1 to 2 weeks following the tick bite; they usually peak during the third to sixth week after disease onset, and then demonstrate a gradual decline over a period of months. IgM antibody may persist for months following completion of treatment. IgM antibody results against B burgdorferi should only be considered during the 30 days following exposure and symptom onset. Negative specimens typically demonstrate antibodies to fewer than 2 of the 3 significant B burgdorferi proteins. Additional specimens should be submitted in 2 to 3 weeks if B burgdorferi exposure has not been ruled out. IgG: IgG antibodies to B burgdorferi can be detected approximately 2 weeks after onset of disease and can remain detectable for months to years following completion of therapy. Normal specimens and false-positive EIA specimens generally have antibodies to 4 or fewer proteins. Except for early patients, antibodies from patients with Lyme disease generally bind to 5 or more proteins.

**Reference Values:**
IgG: Negative
IgM: Negative


**ELYME 65417**

**Lyme Disease European Antibody Screen, Serum**

**Clinical Information:** Lyme disease (LD) is caused by infection with a member of the Borrelia burgdorferi sensu lat complex. Among the genospecies within this complex, B burgdorferi sensu stricto (B burgdorferi) is the primary agent causing LD in North America. While B burgdorferi is also found abroad, B garinii and B afzelii are more prevalent in Europe and regions of Asia. These spirochetes are transmitted to humans through the bite of Ixodes species ticks, primarily I ricinus and to a lesser extent I persulcatus, which are both found throughout Europe, the Baltic regions, and parts of Asia. Therefore, residents of or travelers to these areas who are bitten by ticks are at increased risk for LD caused by a European Borrelia species. Transmission of LD-associated Borrelia requires at least 36 hours of tick attachment. Approximately 80% of infected individuals will develop a unique expanding skin lesion with a central zone of clearing, referred to as erythema migrans (EM; stage 1). In the absence of treatment, patients may progress to early disseminated disease (stage 2), which is characterized by neurologic manifestations (eg, meningitis, cranial neuropathy, radiculoneuropathy) and is often associated with B garinii infection. Patients with late LD often present with intermittent or persistent arthralgia, most often associated with B burgdorferi infection, or with acrodermatitis chronica atrophicans (ACA), typically due to infection with B afzelii. Diagnosis of LD is currently based on a 2-tiered serologic testing algorithm to detect antibodies to LD-associated Borrelia species. Importantly, patients may be seronegative until 2 weeks postonset of symptoms. An IgM-class antibody response usually peaks between 3 to 6 weeks after
infection, but may persist for years in some cases. IgG-class antibodies to Borrelia spirochetes are detectable 2 to 3 weeks postinfection and may remain elevated for years after resolution of symptoms. In patients with EM, culture of skin biopsies obtained near the margins of the rash, are frequently positive, though this technique is not commonly available. In late (chronic) stages of the disease, serology is often positive and is the diagnostic method of choice. Polymerase chain reaction (PCR) testing may also be of use in these late stages if performed on synovial fluid or tissue. Early antibiotic treatment of Lyme disease can resolve clinical symptoms and prevent progression of the disease to later stages. Also, if provided early in disease, treatment may suppress the immune response to the bacteria leading to negative serologic results. The 2-tiered testing algorithm for LD involves an initial screening assay for detection of total antibodies to LD-causing Borrelia species. For this algorithm, the C6 enzyme-linked immunosorbent assay (ELISA) is used to screen all specimens and those with positive or equivocal are reflexed for supplemental testing by immunoblot for detection of IgM and IgG antibodies to LD-causing Borrelia species. Importantly, while most screening ELISAs detect antibodies to all major LD-associated Borrelia species, the immunoblots used for supplemental testing in North America are specifically designed to detect antibodies to the B burgdorferi B31 strain. Despite similarity between the genospecies, the North America immunoblots have a reported sensitivity of approximately 50% for LD caused by the European Borrelia species (eg, B afzelii and B garinii). In order to improve upon our ability to detect antibodies to the European Borrelia species, immunoblots designed to detect IgM- and IgG-class antibodies B garinii, B afzelii and B burgdorferi are used for supplemental testing of all specimens with positive or equivocal results by the LD screening ELISA.

**Useful For:** Aids in diagnosis of Lyme disease caused by infection with Borrelia species endemic to Europe and Asia, including B garinii and B afzelii. This test is only intended for use in patients with recent travel to and exposure to ticks in Europe or regions of Asia who are suspected to have Lyme disease caused by Borrelia species endemic to Europe/Asia.

**Interpretation:**
- **Negative result:** No antibodies to Lyme disease Borrelia species (eg B afzelii, B burgdorferi, B garinii) detected. Repeat testing on a new specimen collected in 2 to 3 weeks should be considered if acute Lyme disease due to one of these Borrelia species is suspected. 
- **Equivocal result:** Not diagnostic. Supplemental immunoblot testing has been ordered by reflex.
- **Positive result:** Not diagnostic. Supplemental immunoblot testing has been ordered by reflex.

**Reference Values:**
- **Negative**

**Clinical References:**
2-tiered serologic testing algorithm to detect antibodies to LD-associated Borrelia species. Importantly, patients may be seronegative until 2 weeks postonset of symptoms. An IgM-class antibody response usually peaks between 3 to 6 weeks after infection, but may persist for years in some cases. IgG-class antibodies to Borrelia spirochetes are detectable 2 to 3 weeks postinfection and may remain elevated for years after resolution of symptoms. In patients with EM, culture of skin biopsies obtained near the margins of the rash, are frequently positive, though this technique is not commonly available. In late (chronic) stages of the disease, serology is often positive and is the diagnostic method of choice. Polymerase chain reaction (PCR) testing may also be of use in these late stages if performed on synovial fluid or tissue. Early antibiotic treatment of Lyme disease can resolve clinical symptoms and prevent progression of the disease to later stages. Also, if provided early in disease, treatment may suppress the immune response to the bacteria leading to negative serologic results. The 2-tiered testing algorithm for LD involves an initial screening assay for detection of total antibodies to LD-causing Borrelia species. For this algorithm, the C6 ELISA is used to screen all specimens and those with positive or equivocal results are reflexed for supplemental testing by immunoblot for detection of IgM and IgG antibodies to LD-causing Borrelia species. Importantly, while most screening ELISAs detect antibodies to all major LD-associated Borrelia species, the immunoblots used for supplemental testing in North America are specifically designed to detect antibodies to the B burgdorferi B31 strain. Despite similarity between the genospecies, the North America immunoblots have a reported sensitivity of approximately 50% for LD caused by the European Borrelia species (eg, B afzelii and B garinii). In order to improve upon our ability to detect antibodies to the European Borrelia species, immunoblots designed to detect IgM and/or IgG-class antibodies B garinii, B afzelii, and B burgdorferi are used for supplemental testing of all specimens with positive or equivocal results by the LD screening ELISA.

**Useful For:** Aids in diagnosis of Lyme disease caused by infection with Borrelia species endemic to Europe and Asia, including B garinii or B afzelii. This test is only intended for use in patients with recent travel to and exposure to ticks in Europe or regions of Asia who are suspected to have Lyme disease caused by Borrelia species endemic to Europe/Asia.

**Interpretation:** IgM: The interpretation of IgM immunoblots for Lyme disease caused by Borrelia species endemic to Europe differs from the interpretive criteria for IgM immunoblots used for evaluation of Lyme disease caused by B burgdorferi in North America. The European Lyme disease IgM immunoblot interpretive criteria is as follows: Positive: The presence of a band at 1 or more of the following 5 proteins - p39, OspC, Osp17 (DbpA), VlsE, and/or p41 (high intensity) Interpretation: Specific antibodies against Lyme disease associated Borrelia species detected suggesting recent infection. Negative: No distinct bands Interpretation: No specific antibodies against Lyme disease associated Borrelia species were detected. If infection remains suspected, repeat testing on a new specimen collected in 2 to 3 weeks is suggested. IgM-class antibodies to Borrelia species that cause Lyme disease, including B afzelii and B garinii, may be detectable as early as 1 to 2 weeks following a tick bite, however, they typically peak during the third to sixth week postinfection. IgM-class antibodies to these agents may persist for months following disease resolution and antimicrobial treatment. Results of the IgM immunoblot should only be interpreted and considered during the first 4 to 6 weeks after disease onset. Patients tested soon after disease onset may be negative for IgM-class antibodies to Lyme disease-associated Borrelia species. Repeat testing should be performed in 2 to 3 weeks if infection with a European species of Borrelia continues to be suspected. IgG: The interpretation of IgG immunoblots for Lyme disease caused by Borrelia species endemic to Europe differs from the interpretive criteria for IgG immunoblots used to for evaluation of Lyme disease caused by B burgdorferi in North America. The European Lyme disease IgG immunoblot is interpreted as follows: Positive: The presence of a band at 2 or more of the following 10 proteins: p38, p58, p43, p39, p30, OspC, p21, Osp17(Dbpa), p14, VlsE Interpretation: Specific antibodies against Lyme disease associated Borrelia species were detected, suggesting infection at some point in the recent or remote past. Clinical correlation required. Equivocal: One distinct band at the VlsE protein only Interpretation: Specific antibodies to the VlsE protein of Lyme disease associated Borrelia species were detected, suggesting possible infection. Repeat testing on a new specimen collected in 2 to 3 weeks is recommended to confirm infection. Negative: One or no distinct bands (except VlsE) Interpretation: No specific antibodies against Lyme disease-associated Borrelia species were detected. If infection remains suspected, repeat testing on a new specimen collected in 2 to 3 weeks is suggested. IgG-class antibodies to Lyme disease causing Borrelia species may remain detectable for months to years following resolution of disease and/or antimicrobial treatment.
LYME
9129

**Lyme Disease Serology, Serum**

**Clinical Information:** Lyme disease (LD) is caused by infection with a member of the Borrelia burgdorferi sensu lato complex, which includes B burgdorferi sensu stricto (herein referred to as B burgdorferi), B afzelii, and B garinii. Among these species, B burgdorferi is the most frequent cause of LD in North America. These tick-borne spirochetes are transmitted to humans through the bite of Ixodes species ticks. Endemic areas for Lyme disease in the United States correspond with the distribution of 2 tick species, Ixodes scapularis (Northeastern and Upper Midwestern US) and I pacificus (West Coast US). Transmission of LD-associated Borrelia requires at least 36 hours of tick attachment. Approximately 80% of infected individuals will develop a unique expanding skin lesion with a central zone of clearing, referred to as erythema migrans (EM; stage 1). In the absence of treatment, patients may progress to early disseminated disease (stage 2), which is characterized by neurologic manifestations (eg, meningitis, cranial neuropathy, radiculoneuropathy) and is often associated with B garinii infection. Patients with late LD often present with intermittent persistent arthralgia, most often associated with B burgdorferi infection, or with acrodermatitis chronica atrophicans (ACA), typically due to infection with B afzelii. Diagnosis of LD is currently based on a 2-tiered serologic testing algorithm, as recommended by the Centers for Disease Control and Prevention (CDC), and involves an initial screening assay for detection of antibodies to LD-causing Borrelia species. Samples that are screen positive or equivocal are subsequently reflexed for supplemental assessment using a B burgdorferi immunoblot for detection of IgM- and IgG-class antibodies to specific B burgdorferi antigens. Importantly, while serologic assessment for LD may be negative in the early weeks following infection, over 90% of patients with later stages of infection are seropositive by serology, which remains the diagnostic method of choice for this disease.

**Useful For:** Diagnosis of Lyme disease

**Interpretation:** Negative: No evidence of antibodies to Borrelia burgdorferi detected. False-negative results may occur in recently infected patients (< or =2 weeks) due to low or undetectable antibody levels to B burgdorferi. If recent exposure is suspected, a second sample should be collected and tested in 2 to 4 weeks. Equivocal: Not diagnostic. Supplemental testing by immunoblot has been ordered by reflex. Positive: Not diagnostic. Supplemental testing by immunoblot has been ordered by reflex.

**Reference Values:**

Negative
Reference values apply to all ages.

**Clinical References:**

PBORR
80574

**Lyme Disease, Molecular Detection, PCR**

**Clinical Information:** Lyme disease is a multisystem and multistage tick-transmitted infection caused by spirochetal bacteria in the Borrelia burgdorferi sensu lato (Bbsl) complex.(1) Nearly all human infections are caused by 3 Bbsl species; B burgdorferi sensu stricto (hereafter referred to as B burgdorferi) is the primary cause of Lyme disease in North America, while B afzelii and B garinii are the primary causes of Lyme disease in Europe. In 2012, B mayonii has been identified as a less common
cause of Lyme disease in the upper Midwestern United States. This organism has only been detected in patients with exposure to ticks in Minnesota and Wisconsin and has not been detected in over 10,000 specimens from patients in other states including regions of northeast where Lyme disease is endemic. Lyme disease is the most commonly reported tick-borne infection in Europe and North America, causing an estimated 300,000 cases in the United States each year, and 85,000 cases in Europe. The clinical features of Lyme disease are broad and may be confused with various immune and inflammatory disorders. The classic presenting sign of early localized Lyme disease caused by B. burgdorferi is erythema migrans (EM), which occurs in approximately 80% of individuals. Other early signs and symptoms include malaise, headache, fever, lymphadenopathy, and myalgia. Arthritis, neurological disease, and cardiac disease may be later stage manifestations. Erythema migrans has also been seen in patients with B. mayonii infection, but diffuse rashes are more commonly reported. The chronic skin condition, acrodermatitis chronica atrophicans, is also associated with B. afzelii infection. The presence of EM in the appropriate clinical setting is considered diagnostic for Lyme disease and no confirmatory laboratory testing is needed. In the absence of a characteristic EM lesion, serologic testing is the diagnostic method of choice for Lyme disease. However, serology may not be positive until 1 to 2 weeks after onset of symptoms, and may show decreased sensitivity for detection of infection with B. mayonii. Therefore, detection of Bbsl DNA using PCR may be a useful adjunct to serologic testing for detection of acute disease. PCR has shown utility for detection of Borrelia DNA from skin biopsies of Lyme-associated rashes and also be used to detect Borrelia DNA from synovial fluid and synovium biopsies. Less commonly, Borrelia DNA can be detected in cerebrospinal fluid. Lyme PCR should always be performed in conjunction with FDA-approved serologic tests, and the results should be correlated with serologic and epidemiologic data and clinical presentation of the patient. The Mayo Clinic Lyme PCR test detects and differentiates the main causes of Lyme disease in North America (B. burgdorferi and B. mayonii) and Europe (B. afzelii and B. garinii). 

**Useful For:** Supporting the diagnosis of Lyme disease in conjunction with serologic testing. Specific indications including testing skin biopsies when a rash lesion is not characteristic of erythema migrans, and testing synovial fluid or synovium to support the diagnosis of Lyme arthritis.

**Interpretation:** A positive result indicates the presence of DNA from Borrelia burgdorferi, B. mayonii, B. afzelii, or B. garinii, the main agents of Lyme disease. A negative result indicates the absence of detectable target DNA in the specimen. Due to the clinical sensitivity limitations of the PCR assay, a negative result does not preclude the presence of the organism or active Lyme disease.

**Reference Values:**

**Negative**

**Clinical References:**

infections are caused by 3 Bbsl species; Borrelia burgdorferi sensu stricto (hereafter referred to as Borrelia burgdorferi) is the primary cause of Lyme disease in North America, while Borrelia afzelii and Borrelia garinii are the primary causes of Lyme disease in Europe. Recently, Candidatus Borrelia mayonii has been identified as a second cause of Lyme disease in the United States.(2) Only 6 cases of Borrelia mayonii infection have been described to date, and all patients reported exposure to ticks in Minnesota or Wisconsin. Lyme disease is the most commonly reported tick-borne infection in Europe and North America, causing an estimated 300,000 cases in the United States each year, and 85,000 cases in Europe.(3,4) The clinical features of Lyme disease are broad and may be confused with various immune and inflammatory disorders. The classic presenting sign of early localized Lyme disease caused by Borrelia burgdorferi is erythema migrans (EM), which occurs in approximately 80% of individuals. Other early signs and symptoms include malaise, headache, fever, lymphadenopathy, myalgia, and arthralgia. Arthritis, neurological disease, and cardiac disease may be later stage manifestations. The chronic skin condition, acrodermatitis chronicum atrophicans, is also associated with Borrelia afzelii infection. The presence of EM in the appropriate clinical setting is considered diagnostic for Lyme disease and no confirmatory laboratory testing is needed. In the absence of a characteristic EM lesion, serologic testing is the diagnostic method of choice for Lyme disease.(5) However, serology may not be positive until 2 to 4 weeks after onset of symptoms, and may show decreased sensitivity for detection of infection with Borrelia mayonii. Therefore, detection of Bbsl DNA using PCR may be a useful adjunct to serologic testing for detection of acute disease. PCR has shown utility for detection of Borrelia DNA from skin biopsies of EM lesions, as well as DNA from synovial and cerebrospinal fluid in late-stage disease. Borrelia DNA can also, rarely, be detected from blood.(6) In general, blood is not the preferred source for detection of Bbsl DNA by PCR, although it may have increased utility for detection of Borrelia mayonii, due to the higher levels of observed peripheral spirochetemia with this organism.(2,6) Lyme PCR should always be performed in conjunction with FDA-approved serologic tests, and results should be correlated with serologic and epidemiologic data and clinical presentation of the patient. The Mayo Clinic Lyme PCR test detects and differentiates the causes of Lyme disease in North America (Borrelia burgdorferi and Borrelia mayonii) and Europe (Borrelia afzelii and Borrelia garinii).

**Useful For:** Confirmation of active Lyme disease

**Interpretation:** A positive result indicates the presence of DNA from Borrelia burgdorferi, Borrelia mayonii, Borrelia afzelii, or Borrelia garinii, the agents of Lyme disease. A negative result indicates the absence of detectable target DNA in the specimen. Due to the diagnostic sensitivity limitations of the PCR assay, a negative result does not preclude the presence of the organism or active Lyme disease.

**Reference Values:**
Negative

**Clinical References:**
phytohemagglutinin) has been assessed. The anti-CD3 proliferation panel is not a first-level test for

Useful For:

When serially monitoring patients for lymphocyte subsets.

These data, therefore, indicate that timing, and consistency in timing, of blood collection is critical
in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol
Natural killer (NK)-cell counts, on the other hand, is constant throughout the day. Circadian variations
demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and
subsets are known to be influenced by a variety of biological factors, including hormones, the
cytometry using 7-aminoactinomycin D (7-AAD) and annexin V. The absolute counts of lymphocyte
addition of cell-specific antibodies. Cell viability, apoptosis, and death can also be measured by flow cytometry.(9) Specific proliferating cell populations can be visualized by the
covalent bond is formed between the dye and the incorporated nucleotide, and the fluorescent signal is
subsequently fixed, permeabilized, and reacted with a dye-labeled azide, catalyzed by copper. A
covalent bond is formed between the dye and the incorporated nucleotide, and the fluorescent signal is
then measured by flow cytometry.(9) Specific proliferating cell populations can be visualized by the
addition of cell-specific antibodies. Cell viability, apoptosis, and death can also be measured by flow cytometry using 7-aminoactinomycin D (7-AAD) and annexin V. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have
been shown to be critical in T-cell proliferation.(4,5) The interaction of IL-2 with the IL-2 receptor (IL-2R) plays a central role in regulation of T-cell proliferation.(4) Triggering of the TCR leads to synthesis of IL-2 in certain T-cell subsets and induction of high-affinity IL-2Rs in antigen- or mitogen-activated T cells, and the binding of IL-2 to IL-2R ultimately leads to T-cell proliferation. The use of exogenous IL-2 in association with anti-CD3 allows discrimination of whether T cells, which cannot proliferate to other mitogenic signals, can respond to a potent growth factor such as IL-2. Stimulation of T cells with soluble antibodies to anti-CD3 (and the associated TCR complex) causes mobilization of cytoplasmic calcium and translocation of protein kinase C from the cytoplasm to the cell membrane. This stimulation also causes induction of phosphatidylinositol metabolism and subsequent IL-2 production for proliferation.(6) T-cell activation induced by anti-CD3 antibody requires prolonged stimulation of protein kinase C, which apparently can be achieved by the concomitant use of the anti-CD28 antibody for costimulation without addition of other mitogenic stimuli, such as phorbol myristate acetate (PMA).(7) This assay uses a method that directly measures the S-phase proliferation of lymphocytes through the use of click chemistry. In the Invitrogen Click-iT-EdU assay, the click chemistry has been adapted to measure cell proliferation through direct detection of nucleotide incorporation. The Click-iT-EdU assay has been shown to be an acceptable alternative to the 3H-thymidine assay for measuring lymphocyte/T-cell proliferation.(8) In the assay, an alkyn-modified nucleoside is supplied in cell-growth media for a defined time period and is incorporated within cells. The cells are subsequently fixed, permeabilized, and reacted with a dye-labeled azide, catalyzed by copper. A
covalent bond is formed between the dye and the incorporated nucleotide, and the fluorescent signal is
then measured by flow cytometry.(9) Specific proliferating cell populations can be visualized by the
addition of cell-specific antibodies. Cell viability, apoptosis, and death can also be measured by flow cytometry using 7-aminoactinomycin D (7-AAD) and annexin V. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer (NK)-cell counts, on the other hand, is constant throughout the day. Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration. In fact, cortisol and catecholamine concentrations control distribution and, therefore, the numbers of naive versus effector CD4 and CD8 T cells. It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening, and during summer compared to winter. These data, therefore, indicate that timing, and consistency in timing, of blood collection is critical when serially monitoring patients for lymphocyte subsets.

Useful For: A second-level test after lymphocyte proliferation to mitogens (specifically phytohemagglutinin) has been assessed. The anti-CD3 proliferation panel is not a first-level test for
assessing lymphocyte (T-cell) function Evaluating patients suspected of having impairment in cellular immunity Evaluation of T-cell function in patients with primary immunodeficiencies, either cellular (DiGeorge syndrome, T-negative severe combined immunodeficiency [SCID], etc) or combined T- and B-cell immunodeficiencies (T- and B-negative SCID, Wiskott Aldrich syndrome, ataxia telangiectasia, common variable immunodeficiency, among others) where T-cell function may be impaired Evaluation of T-cell function in patients with secondary immunodeficiency, either disease related or iatrogenic Evaluation of recovery of T-cell function and competence following bone marrow transplantation or hematopoietic stem cell transplantation Evaluation of T-cell function in patients receiving immunosuppressive or immunomodulatory therapy Evaluation of T-cell function in the context of identifying neutralizing antibodies in patients receiving therapeutic anti-CD3 antibody immunosuppression for solid organ transplantation or autoimmune diseases, such as type 1 diabetes

Interpretation: Abnormal test results to anti-CD3/aCD28/interleukin-2 (IL-2) stimulation are indicative of impaired T-cell function if T-cell counts are normal or only modestly decreased. If there is profound T-cell lymphopenia, it must be kept in mind that there could be a "dilution" effect with underrepresentation of T cells within the peripheral blood mononuclear cells (PBMC) population that could result in lower T-cell proliferative responses. However, this is not a significant concern in the flow cytometry assay, since acquisition of additional cellular events during analysis can compensate for artificial reduction in proliferation due to lower T-cell counts. The evaluation of T-cell proliferation to anti-CD3/IL-2 is likely to be helpful in assessing T-cell function in patients with refractory responses to other mitogenic and antigenic stimuli, specifically in the context of IL-2-receptor signaling defects, enabling greater mechanistic insight into the origins of T-cell dysfunction. There is no absolute correlation between T-cell proliferation in vitro and a clinically significant immunodeficiency, whether primary or secondary, since T-cell proliferation in response to activation is necessary, but not sufficient, for an effective immune response. Therefore, the proliferative response to any mitogenic stimulus, including anti-CD3/anti-CD28, can be regarded as a more specific but less sensitive test for the diagnosis of infection susceptibility. It should also be kept in mind that there is no single laboratory test that can identify or define impaired cellular immunity, with the exception of identification of an opportunistic infection. Controls in this laboratory and most clinical laboratories are healthy adults. Since this test is used for screening and evaluating cellular immune dysfunction in infants and children, it is reasonable to question the comparability of proliferative responses between healthy infants, children, and adults. One study has reported that the highest mitogen responses are seen in newborn infants with subsequent decline to 6 months of age, and a continuing decline through adolescence to half the neonatal response. In our evaluation of 43 pediatric samples (of all ages) with adult normal controls, only 21% and 14% were below the tenth percentile of the adult reference range for the mitogens, pokeweed mitogen (PWM) and phytohemagglutinin (PHA), respectively. Comparisons between pediatric and adult data have not been performed for anti-CD3/aCD28 due to unavailability of prospective blood samples from healthy or patient pediatric donors for purposes of analytical validation. It should be noted that without obtaining formal pediatric reference values it remains a possibility that the response in infants and children can be underestimated. However, the practical challenges of generating a pediatric range for this assay necessitate comparison of pediatric data with adult reference values or controls. Lymphocyte proliferation responses to mitogens (including anti-CD3 stimulation) and antigens are significantly affected by time elapsed since blood collection. Results have been shown to be variable for specimens assessed greater than 24 and less than 48 hours post blood collection; therefore, lymphocyte proliferation results must be interpreted with due caution and results should be correlated with clinical context.

Reference Values:
Viability of lymphocytes at day 0: > or =75.0%
Maximum proliferation of anti-CD3 as % CD45: > or =19.4%
Maximum proliferation of anti-CD3 as % CD3: > or =20.3%
Maximum proliferation of anti-CD3 + anti-CD28 as % CD45: > or =37.5%
Maximum proliferation of anti-CD3 + anti-CD28 as % CD3: > or =44.6%
Maximum proliferation of anti-CD3 + IL-2 as % CD45: > or =41.7%
Maximum proliferation of anti-CD3 + IL-2 as % CD3: > or =46.2%


Lymphocyte Proliferation to Antigens, Blood

Clinical Information: Determining impaired T-cell function by culturing human peripheral blood mononuclear cells (PBMC) in vitro with recall antigens, including Candida albicans (CA) and tetanus toxoid (TT), has been part of the diagnostic immunology repertoire for many years.\(^1,2\) The widely used method for assessing lymphocyte proliferation to antigens has hitherto been the measurement of 3H-thymidine incorporated into the DNA of proliferating cells. The disadvantages with the 3H-thymidine method of lymphocyte proliferation are: 1. The technique is cumbersome due to the use of radioactivity 2. It does not allow discrimination of responding cell populations in response to stimulation 3. It does not provide any information on contribution of activation-induced cell death to the interpretation of the final result Further, decreased lymphocyte proliferation could be due to several factors, including overall diminution of T-cell proliferation or decrease in proliferation of only a subset of T cells, or an apparent decrease in total lymphocyte proliferation due to T-cell lymphopenia and under representation of T cells in the PBMC pool. None of these can be discriminated by the thymidine uptake assay, but can be assessed by flow cytometry, which uses antibodies to identify specific responder cell populations. Cell viability can also be measured within the same assay without requiring additional cell manipulation or sample. Antigens, like CA and TT, have been widely used to measure antigen-specific recall (anamnestic) T-cell responses when assessing cellular immunity. In fact, it may be more revealing about cellular immune compromise than assessing the response of lymphocytes to mitogens because the latter can induce T-cell proliferative responses even if those T cells are incapable of responding adequately to antigenic (physiologic) stimuli. Therefore, abnormal T-cell responses to antigens are considered a diagnostically more sensitive, but less specific, test of aberrant T-cell function.\(^2\) Antigens used in recall assays measure the ability of T cells bearing specific T-cell receptors (TCR) to respond to such antigens when processed and presented by antigen-presenting cells. The antigens used for assessment of the cellular immune response are selected to represent antigens, seen by a majority of the population, either through natural exposure (CA) or as a result of vaccination (TT). This assay uses a method that directly measures the S-phase proliferation of lymphocytes through the use of click chemistry. Cell viability, apoptosis, and death can also be measured by flow cytometry using 7-AAD and Annexin V. The Click-iT-EdU assay has already been shown to be an acceptable alternative to the 3H-thymidine assay for measuring lymphocyte/T-cell proliferation.\(^3\) The degree of impairment of antigen-specific T-cell responses can vary depending on the nature of the cellular immune compromise. For example, some, but not all, patients with partial DiGeorge syndrome, a primary cellular immunodeficiency, have been reported to have either decreased or absent T-cell responses to CA and TT.\(^4\) Similarly, relative immune compromise, especially to TT, has been reported in children with vitamin A deficiency, but the measurements have been largely of the humoral immune response. Since this requires participation of the cellular immune compartment, it can be postulated that there could be a potential impairment of antigen-specific T-cell responses as well.\(^5\)

Useful For: Assessing T-cell function in patients on immunosuppressive therapy, including solid-organ
transplant patients Evaluating patients suspected of having impairment in cellular immunity Evaluation of T-cell function in patients with primary immunodeficiencies, either cellular (DiGeorge syndrome, T-negative severe combined immunodeficiency: SCID, etc) or combined T- and B-cell immunodeficiencies (T- and B-negative SCID, Wiskott Aldrich syndrome, ataxia telangiectasia, common variable immunodeficiency, among others) where T-cell function may be impaired Evaluation of T-cell function in patients with secondary immunodeficiency, either disease related or iatrogenic Evaluation of recovery of T-cell function and competence following bone marrow transplantation or hematopoietic stem cell transplantation

**Interpretation:** Abnormal test results to antigen stimulation are indicative of impaired T-cell function, if T-cell counts are normal or only modestly decreased. If there is profound T-cell lymphopenia, it must be kept in mind that there could be a "dilution" effect with underrepresentation of T cells within the peripheral blood mononuclear cell (PBMC) population that could result in lower T-cell proliferative responses. However, this is not a significant concern in the flow cytometry assay, since acquisition of additional cellular events during analysis can compensate for artificial reduction in proliferation due to lower T-cell counts. In the case of antigen-specific T-cell responses to tetanus toxoid (TT), there can be absent responses due to natural waning of cellular immunity, if the interval between vaccinations has exceeded the recommended period, especially in adults. In such circumstances, it would be appropriate to measure TT-specific T-cell responses 4 to 6 weeks after a booster vaccination. There is no absolute correlation between T-cell proliferation in vitro and a clinically significant immunodeficiency, whether primary or secondary, since T-cell proliferation in response to activation is necessary, but not sufficient, for an effective immune response. Therefore, the proliferative response to antigens can be regarded as a more sensitive, but less specific, test for the diagnosis of infection susceptibility. It should also be kept in mind that there is no single laboratory test that can identify or define impaired cellular immunity, with the exception of an opportunistic infection. Controls in this laboratory and most clinical laboratories are healthy adults. Since this test is used for screening and evaluating cellular immune dysfunction in infants and children, it is reasonable to question the comparability of proliferative responses between healthy infants, children, and adults. It is reasonable to expect robust T-cell-specific responses to TT in children without cellular immune compromise, as a result of repeated childhood vaccinations. The response to Candida albicans can be more variable depending on the extent of exposure and age of exposure. A comment will be provided in the report documenting the comparison of pediatric results with an adult reference range and correlation with clinical context for appropriate interpretation. It should be noted that without obtaining formal pediatric reference values, it remains a possibility that the response in infants and children can be underestimated. However, the practical challenges of generating a pediatric range for this assay necessitate comparison of pediatric data with adult reference values or controls.

**Reference Values:**
Viability of lymphocytes at day 0: > or =75.0%

- Maximum proliferation of Candida albicans as % CD45: > or =5.7%
- Maximum proliferation of Candida albicans as % CD3: > or =3.0%
- Maximum proliferation of tetanus toxoid as % CD45: > or =5.2%
- Maximum proliferation of tetanus toxoid as % CD3: > or =3.3%

**Clinical References:**
Lymphocyte Proliferation to Mitogens, Blood

Clinical Information: The method of determining impaired T-cell function by culturing human peripheral blood mononuclear cells (PBMC) in vitro with mitogenic plant lectins (mitogens) such as phytohemagglutinin (PHA) and pokeweed mitogen (PWM) has been part of the diagnostic immunology repertoire for many years.(1,2) The widely used method for assessing lymphocyte proliferation has hitherto been the measurement of 3H-thymidine incorporated into the DNA of proliferating cells. The disadvantages with the 3H-thymidine method of lymphocyte proliferation are: 1. The technique is cumbersome due to the use of radioactivity. 2. It does not allow discrimination of responding cell populations in response to stimulation. 3. It does not provide any information on contribution of activation-induced cell death to the interpretation of the final result. Further, decreased lymphocyte proliferation could be due to several factors, including overall diminution of T-cell proliferation or decrease in proliferation of only a subset of T cells, or an apparent decrease in total lymphocyte proliferation due to T-cell lymphopenia and under-representation of T cells in the PBMC pool. None of these can be discriminated by the thymidine uptake assay, but can be assessed by flow cytometry, which uses antibodies to identify specific responder cell populations. Cell viability can also be measured within the same assay without requiring additional cell manipulation or specimen. Mitogens are very potent stimulators of T-cell activation and proliferation independent of their antigenic specificity.(3) It has been suggested that mitogens can induce T-cell proliferative responses even if they are incapable of responding adequately to antigenic (physiologic) stimuli. Therefore, abnormal T-cell responses to mitogens are considered a diagnostically less sensitive but more specific test of aberrant T-cell function. Lectin mitogens have been shown to bind the T-cell receptor, which is glycosylated through its carbohydrate moiety, thereby activating quiescent T cells. Mitogenic stimulation has been shown to increase intracellular calcium (Ca++) in T cells, which is absolutely essential for T-cell proliferation. While PHA is a strong T-cell mitogen, PWM is a weak T-cell mitogen, but it also induces B-cell activation and proliferation as well. For this assay, we use a method that directly measures the S-phase proliferation of lymphocytes through the use of Click chemistry. In the Invitrogen Click-iT-EdU assay, the Click chemistry has been adapted to measure cell proliferation through direct detection of nucleotide incorporation. In the assay, an alkyne-modified nucleoside is supplied in cell-growth media for a defined time period and is incorporated within cells. The cells are subsequently fixed, permeabilized, and reacted with a dye-labeled azide, catalyzed by copper. A covalent bond is formed between the dye and the incorporated nucleotide, and the fluorescent signal is then measured by flow cytometry.(4) Specific proliferating cell populations can be visualized by the addition of cell-specific antibodies. Cell viability, apoptosis, and death can also be measured by flow cytometry using 7-AAD and Annexin V. The Click-iT-EdU assay has already been shown to be an acceptable alternative to the 3H-thymidine assay for measuring lymphocyte/T-cell proliferation.(5) The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer (NK)-cell counts, on the other hand, are constant throughout the day. Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration. In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells. It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening, and during summer compared to winter. These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

Useful For: Assessing T-cell function in patients on immunosuppressive therapy, including solid-organ transplant patients. Evaluating patients suspected of having impairment in cellular immunity. Evaluation of T-cell function in patients with primary immunodeficiencies, either cellular (DiGeorge syndrome, T-negative severe combined immunodeficiency; SCID, etc) or combined T- and B-cell immunodeficiencies (T- and B-negative SCID, Wiskott Aldrich syndrome, ataxia telangiectasia, common variable immunodeficiency, among others) where T-cell function may be impaired Evaluation of T-cell function in patients with secondary immunodeficiency, either disease related or iatrogenic. Evaluation of recovery of T-cell function and competence following bone marrow transplantation or hematopoietic stem
**Interpretation:** Abnormal test results to mitogen stimulation are indicative of impaired T-cell function if T-cell counts are normal or only modestly decreased. If there is profound T-cell lymphopenia, it must be kept in mind that there could be a "dilution" effect with under-representation of T cells within the peripheral blood mononuclear cell (PBMC) population that could result in lower T-cell proliferative responses. However, this is not a significant concern in the flow cytometry assay, since acquisition of additional cellular events during analysis can compensate for artificial reduction in proliferation due to lower T-cell counts. There is no absolute correlation between T-cell proliferation in vitro and a clinically significant immunodeficiency, whether primary or secondary, since T-cell proliferation in response to activation is necessary, but not sufficient, for an effective immune response. Therefore, the proliferative response to mitogens can be regarded as a more specific but less sensitive test for the diagnosis of infection susceptibility. It should also be kept in mind that there is no single laboratory test that can identify or define impaired cellular immunity, with the exception of an opportunistic infection. Controls in this laboratory and most clinical laboratories are healthy adults. Since this test is used for screening and evaluating cellular immune dysfunction in infants and children, it is reasonable to question the comparability of proliferative responses between healthy infants, children, and adults. One study has reported that the highest mitogen responses are seen in newborn infants with subsequent decline to 6 months of age, and a continuing decline through adolescence to half the neonatal response.(6) In our evaluation of 43 pediatric specimens (of all ages) with adult normal controls, only 21% and 14% were below the tenth percentile of the adult reference range for pokeweed (PWM) and phytohemagglutinin (PHA), respectively. A comment will be provided in the report documenting the comparison of pediatric results with an adult reference range and correlation with clinical context for appropriate interpretation. It should be noted that without obtaining formal pediatric reference values it remains a possibility that the response in infants and children can be underestimated. However, the practical challenges of generating a pediatric range for this assay necessitate comparison of pediatric data with adult reference values or controls. Lymphocyte proliferation responses to mitogens and antigens are significantly affected by time elapsed since blood collection. Results have been shown to be variable for specimens assessed more than 24- and less than 48-hours postblood collection; therefore, lymphocyte proliferation results must be interpreted with due caution and results should be correlated with clinical context.

**Reference Values:**
Viability of lymphocytes at day 0: > or = 75.0%
Maximum proliferation of phytohemagglutinin as % CD45: > or = 49.9%
Maximum proliferation of phytohemagglutinin as % CD3: > or = 58.5%
Maximum proliferation of pokeweed mitogen as % CD45: > or = 4.5%
Maximum proliferation of pokeweed mitogen as % CD3: > or = 3.5%
Maximum proliferation of pokeweed mitogen as % CD19: > or = 3.9%

**Clinical References:**
Clinical Information: Lymphoid enhancer-binding factor 1 (LEF1) is a transcription factor that participates in the activation of genes within the Wnt signaling pathway. LEF1 is expressed by inactive T-cells and a subset of B-cells.

Useful For: Differentiating cancers of B-cell origin

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Lymphoplasmacytic Lymphoma/Waldenstrom Macroglobulinemia (LPL/WM), MYD88 L265P with Reflex to CXCR4

Clinical Information: The MYD88 L265P abnormality is highly associated (>90%) with the pathologic diagnosis of lymphoplasmacytic lymphoma and the clinical syndrome of Waldenstrom macroglobulinemia (LPL/WM), particularly in the setting of an elevated IgM serum monoclonal paraprotein. CXCR4 mutations are identified in approximately 30% to 40% of LPL/WM and are almost always in association with MYD88 L265P, which is highly prevalent in this neoplasm. The status of CXCR4 mutations in the context of MYD88 L265P is clinically relevant as important determinants of clinical presentation, overall survival and therapeutic response to ibrutinib: A MYD88-L265P/CXCR4-WHIM (C-terminus nonsense/frameshift mutations) molecular signature is associated with intermediate to high bone marrow disease burden and serum IgM levels, less adenopathy, and intermediate response to ibrutinib in previously treated patients, a MYD88-L265P/CXCR4-WT (wild type) molecular signature is associated with intermediated bone marrow disease burden and serum IgM levels, more adenopathy, and highest response to ibrutinib in previously treated patients, and the MYD88-WT/CXCR4-WT molecular signature is associated with inferior overall survival, lower response to ibrutinib therapy in previously treated patients, and lower bone marrow disease burden in comparison to those harboring a MYD88-L265 mutation.

Useful For: Establishing the diagnosis of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (LPL/WM) Helping distinguish LPL/WM low-grade B-cell lymphoma from other subtypes Aiding in the prognostication and clinical management of LPL/WM

Interpretation: Mutation present or not detected; an interpretive report will be issued.

Reference Values:
MYD88 L265P: Mutation present or absent based on expected mutant PCR product size for the MYD88 gene (NCBI accession NM_002468.4).

CXCR4: Mutations present or absent in the test region c. 898-1059 (amino acids 300-353) of the CXCR4 gene (NCBI NM_003467.2, GRCh37).

Lynch Syndrome Panel

Clinical Information: While the risk for colorectal cancer in the general population is 6%, rarely colon cancer is attributable to hereditary factors associated with a single abnormal gene that predisposes individuals to increased risks for cancer in a family. Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC) is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3’ end of the EPCAM gene, which lead to inactivation of the MSH2 promotor, have also been associated with Lynch syndrome. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome-related genes. The lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are less than 15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. The National Comprehensive Cancer Network and the American Cancer Society provide recommendations regarding the medical management of individuals with Lynch syndrome.

Useful For: Establishing a diagnosis of Lynch syndrome Identification of familial MLH1, MSH2, MSH6, PMS2, or EPCAM mutations to allow for predictive testing in family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. (1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

**Clinical References:**

**Lysophosphatidylcholines by LC MS/MS, Blood Spot**

**Clinical Information:** This assay measures C20, C22, C24, and C26 lysophosphatidylcholine (LPC) species in dried blood spots by liquid chromatography-tandem mass spectrometry. Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include 2 major subgroups: disorders of peroxisomal biogenesis and single peroxisomal enzyme/transporter defects. Peroxisome biogenesis defects such as Zellweger spectrum syndrome are characterized by defective assembly of the entire organelle, whereas in single enzyme/transporter defects such as X-linked adrenoleukodystrophy, the organelle is intact, but a specific function is disrupted. These disorders are clinically diverse and range in severity from neonatal lethal to later onset milder variants. X-linked adrenoleukodystrophy (X-ALD) is a disorder affecting the nervous system, adrenal cortex, and testis. It is the most common of the peroxisomal disorders, affecting 1 in 17,000 to 1 in 21,000 males. At least 50% of all females who are heterozygotes for X-ALD are symptomatic. A defect in the ABCD1 gene is responsible for the disease. X-ALD shows a wide range of phenotypic expressions. The clinical phenotypes occurring in males can be subdivided in 4 main categories: cerebral inflammatory, adrenomyeloneuropathy (AMN), Addison only, and asymptomatic. The first 2 phenotypes account for almost 80% of the patients, while the frequency of the asymptomatic category diminishes with age and it is very rare after age 40. It is estimated that approximately 50% of heterozygotes develop an AMN-like syndrome. Treatment options are hormone replacement therapy, dietary intervention, or hematopoietic stem cell transplantation. Elevations of C24 lysophosphatidylcholine (LPC) and C26 LPC may be indicative of X-ALD. In 2016, X-ALD was added to the US Recommended Uniform Screening Panel (RUSP), a list of conditions that are nationally recommended for newborn screening by the Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children. Therefore, measurement of LPCs is a useful second-tier test for newborn screening for X-ALD. Zellweger syndrome spectrum (ZSS) is a continuum of severe disorders affecting the nervous system, vision, hearing, and liver function. Most individuals present in infancy, but adult patients have been identified. The prevalence of ZSS is 1 in 50,000. ZSS follows autosomal recessive inheritance. At least 12 different genes have been implicated in ZSS, with approximately 60% to 70% of mutations occurring in PEX1. The clinical phenotypes include Zellweger syndrome, neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease (IRD). Individuals with Zellweger syndrome typically die within the first year of life without making any developmental progress. Individuals with NALD or IRD typically present in childhood with developmental delays, vision loss, hearing loss, and have a much slower disease progression. There is no specific treatment for ZSS. Although ZSS disorders are not a primary disease target for testing, this test will detect infants with these disorders.
Useful For: Second-tier newborn screen for X-linked adrenoleukodystrophy (X-ALD)

Interpretation: An interpretive report is provided. In females: Elevations of C24 LPC or C26 LPC may be indicative of heterozygosity for X-linked adrenoleukodystrophy (X-ALD), or other forms of peroxisomal disorders. In males: Elevations of C24 LPC or C26 LPC may be indicative of X-ALD or other forms of peroxisomal disorders. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on the analysis, independent biochemical (eg, in vitro enzyme assay) or molecular genetic analyses are required.

Reference Values:

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LALB 62954

Lysosomal Acid Lipase, Blood

Clinical Information: Deficiency of lysosomal acid lipase (LAL) results in 2 clinically distinct phenotypes, Wolman disease (WD) and cholesteryl ester storage disease (CESD). Both phenotypes follow an autosomal recessive inheritance pattern and are caused by mutation in the LIPA gene. WD, the early onset phenotype of LAL deficiency, is a lipid storage disorder characterized by vomiting, diarrhea, failure to thrive, abdominal distension, and hepatosplenomegaly. Peripheral blood lymphocytes are vacuolated and foam cells are present in the bone marrow. Approximately 50% of infants have adrenal calcifications. WD typically presents in the first weeks of life and is fatal in infancy. CESD, the late onset phenotype of LAL deficiency, is clinically variable with patients presenting at any age with progressive hepatomegaly and often splenomegaly, leading to microvesicular steatosis and often liver failure. CESD is likely underdiagnosed and frequently diagnosed incidentally after liver pathology reveals findings similar to nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH). Birefringent cholesteryl ester crystals in hepatocytes or Kupffer cells in fresh-frozen tissues are visualized under polarized light and pathognomonic. Elevated total cholesterol, low-density lipoprotein cholesterol, and triglycerides lead to premature atherosclerosis. Historically, treatment options for WD and CESD were limited, but enzyme replacement therapy is now clinically available.

Useful For: Evaluation of patients with a clinical presentation suggestive of lysosomal acid lipase deficiency in blood specimens

Interpretation: Enzyme activity below 1.5 nmol/hour/mL in properly submitted samples is consistent with lysosomal acid lipase deficiency; Wolman disease or cholesteryl ester storage disease. Normal results (> or =21.0 nmol/h/mL) are not consistent with lysosomal acid lipase deficiency.

Reference Values:
> or =21.0 nmol/hour/mL

Clinical References: 1. Bernstein DL, Hulka H, Bialer MG, Desnick RJ: Cholesteryl ester...
LALBS  
62955

Lysosomal Acid Lipase, Blood Spot

**Clinical Information:** Deficiency of lysosomal acid lipase (LAL) results in 2 clinically distinct phenotypes, Wolman disease (WD) and cholesteryl ester storage disease (CESD). Both phenotypes follow an autosomal recessive inheritance pattern and are caused by mutation in the LIPA gene. WD, the early onset phenotype of LAL deficiency, is a lipid storage disorder characterized by vomiting, diarrhea, failure to thrive, abdominal distension, and hepatosplenomegaly. Peripheral blood lymphocytes are vacuolated and foam cells are present in the bone marrow. Approximately 50% of infants have adrenal calcifications. WD typically presents in the first weeks of life and is fatal in infancy. CESD, the late onset phenotype of LAL deficiency, is clinically variable with patients presenting at any age with progressive hepatomegaly and often splenomegaly, leading to microvesicular steatosis and often, liver failure. CESD is likely underdiagnosed and frequently diagnosed incidentally after liver pathology reveals findings similar to nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH). Birefringent cholesteryl ester crystals in hepatocytes or Kupffer cells in fresh-frozen tissues are visualized under polarized light and pathognomonic. Elevated total cholesterol, low-density lipoprotein cholesterol, and triglycerides lead to premature atherosclerosis. Historically, treatment options for WD and CESD were limited, but enzyme replacement therapy is now clinically available.

**Useful For:** Evaluation of patients with a clinical presentation suggestive of lysosomal acid lipase deficiency in blood spot specimens

**Interpretation:** Enzyme activity below 1.5 nmol/hour/mL in properly submitted samples is consistent with lysosomal acid lipase deficiency: Wolman disease or cholesteryl ester storage disease. Normal results (> or =21.0 nmol/hour/mL) are not consistent with lysosomal acid lipase deficiency.

**Reference Values:**
> or =21.0 nmol/h/mL


LDALD  
64907

Lysosomal and Peroxisomal Disorders Newborn Screen, Blood Spot

**Clinical Information:** Lysosomes are intracellular organelles that contain hydrolytic enzymes that degrade a variety of macromolecules. Lysosomal storage disorders are a diverse group of inherited diseases characterized by the intracellular accumulation of macromolecules due to defects in their transport mechanisms across the lysosomal membrane or due to defective lysosomal enzyme function. The accumulation of these macromolecules leads to cell damage and, eventually, organ dysfunction. More than 40 lysosomal storage disorders have been described with a wide phenotypic spectrum. Gaucher disease is an autosomal recessive lysosomal storage disorder caused by a deficiency of the enzyme, beta-glucosidase. Beta-glucosidase facilitates the lysosomal degradation of glucosylceramide (glucocerebroside) and glucosylsphingosine (glucosylsphingosine). Gaucher disease is caused by mutations in the GBA gene. There are 3 described types of Gaucher disease with varying clinical presentations and age of onset from a perinatal lethal disorder to an asymptomatic type. Features of all types of Gaucher disease include hepatosplenomegaly and hematological abnormalities. Treatment is available in the form of enzyme replacement therapy, substrate reduction therapy, and chaperone therapy for types 1 and 3. Currently, only supportive therapy is available for type 2. Niemann-Pick types A and B are caused by a deficiency of sphingomyelinase due to mutations in the SMPD1 gene. The result is extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and, to a lesser degree, brain. Classification of
type A versus type B is based on the age of onset as well as the severity of symptoms. Niemann-Pick type A disease is more severe and characterized by early onset with feeding problems, dystrophy, persistent jaundice, cherry red maculae, development of hepatosplenomegaly, neurological deterioration, deafness, and blindness, leading to death by age 3. Niemann-Pick type B disease is limited to visceral symptoms with survival into adulthood. Some patients have been described with intermediary phenotypes. Characteristic of the disease are large lipid-laden foam cells on bone marrow biopsy. The combined prevalence of the 2 types is estimated to be 1 in 250,000. Treatment is supportive, although there are clinical trials in place. Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme alpha-glucosidase (GAA; acid maltase) due to mutations in the GAA gene. The estimated incidence is 1 in 40,000 live births. In Pompe disease, glycogen that is taken up by lysosomes during physiologic cell turnover accumulates, causing lysosomal swelling, cell damage, and, eventually, organ dysfunction. The clinical presentation of Pompe disease ranges from a rapidly progressive infantile variant, which is uniformly lethal if untreated, to a more slowly progressive late-onset variant. All disease variants are eventually associated with progressive muscle weakness and respiratory insufficiency. Cardiomyopathy is associated almost exclusively with the infantile form. Enzyme replacement therapy is available for all variants and should be started as soon as possible for patients with the infantile variant and at the first signs of muscle weakness in the later onset variants. Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by mutations in the GALC gene resulting in a deficiency of galactocerebrosidase (GALC, galactosylceramide beta-galactosidase). Galactosylceramide (as with sulfated galactosylceramide) is a lipid component of myelin. The absence of GALC results in globular, distended, multinucleated bodies in the basal ganglia, pontine nuclei, and cerebral white matter. There is severe demyelination throughout the brain with progressive cerebrolegary degenerative disease affecting primarily the white matter. Patients with this early infantile-onset variant of Krabbe disease (<1 in 250,000 live births) die within 2 years. Late infantile-onset Krabbe disease manifests between 6 and 12 months of life and leads to death within a few years as well. Juvenile and adult onset variants present later in life, progress more slowly and, based on newborn screening experience in New York, appear to be more common than the earlier onset variants. Of note, Krabbe disease variants, including pseudodeficiency, may not be discriminated by enzyme activity measurement. Molecular genetic analysis of the GALC gene may provide information on expected age of first symptoms. Psychosine has been shown to be elevated in patients with clinical signs and symptoms of disease and therefore, may be a useful biomarker for the presence of disease or disease progression. The only available therapy is hematopoietic stem cell transplantation that is best performed prior to the onset of clinical symptoms. Early infantile Krabbe disease must, therefore, be considered a critical, time-sensitive newborn screening condition. Fabry disease, caused by mutations in the GLA gene, is an X-linked recessive disorder with an incidence of approximately 1 in 50,000 males. Symptoms result from a deficiency of the enzyme alpha-galactosidase A (GLA; ceramide trihexosidase). Reduced GLA activity results in accumulation of glycosphingolipids in the lysosomes of both peripheral and visceral tissues. Severity and onset of symptoms are dependent on the residual GLA activity. Males with less than 1% GLA activity have the classic form of Fabry disease. Symptoms can appear in childhood or adolescence and usually include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, and corneal opacity. Renal insufficiency, leading to end-stage renal disease and cardiac and cerebrovascular disease, generally occur in middle age. Males with more than 1% GLA activity may present with a variant form of Fabry disease. The renal variant generally has onset of symptoms in the third decade. The most prominent feature in this form is renal insufficiency and, ultimately, end stage renal disease. Individuals with the renal variant may or may not share other symptoms with the classic form of Fabry disease. Individuals with the cardiac variant are often asymptomatic until they present with cardiac findings such as cardiomyopathy or mitral insufficiency in the fourth decade. The cardiac variant is not associated with renal failure. Females who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. Pseudodeficiency alleles may also be detected by newborn screening. Treatment with enzyme replacement therapy (ERT) is available for both males and females with Fabry disease. Mucopolysaccharidosis I (MPS-I) is an autosomal recessive disorder caused by a reduced or absent activity of the alpha-L-iduronidase enzyme. Reduced IDUA activity results in accumulation of glycosaminoglycans (mucopolysaccharides) within the lysosome. The clinical presentation and severity of symptoms of MPS I are variable, ranging from severe disease to attenuated variants (historically known as Hurler-Scheie disease and Scheie disease) that generally present with a later onset and a milder clinical presentation. In general, symptoms may include coarse faces, progressive dysostosis multiplex, hepatosplenomegaly, corneal clouding, hearing loss, mental retardation or learning difficulties, and cardiac valvular disease. MPS-I is caused by mutations in the IDUA gene and
has an estimated incidence of approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. Peroxisomes are organelles present in all human cells except mature erythrocytes. They perform essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCFA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisomal disorders include 2 major subgroups: disorders of peroxisomal biogenesis and single peroxisomal enzyme/transporter defects. Peroxisome biogenesis defects such as Zellweger spectrum syndrome are characterized by defective assembly of the entire organelle, whereas in single enzyme/transporter defects such as X-linked adrenoleukodystrophy, the organelle is intact, but a specific function is disrupted. These disorders are clinically diverse and range in severity from neonatal lethal to later onset milder variants. X-linked adrenoleukodystrophy (XALD) is a disorder affecting the nervous system, adrenal cortex, and testis. It is the most common of the peroxisomal disorders, affecting 1 in 17,000 to 1 in 21,000 males. At least 50% of all females who are heterozygotes for XALD are asymptomatic. A defect in the ABCD1 gene is responsible for the disease. X-ALD shows a wide range of phenotypic expressions. The clinical phenotypes occurring in males can be subdivided in 4 main categories: cerebral inflammatory, adrenomyeloneuropathy (AMN), Addison only, and asymptomatic. The first 2 phenotypes account for almost 80% of the patients, while the frequency of the asymptomatic category diminishes with age and it is very rare after age 40. It is estimated that approximately 50% of heterozygotes develop an AMN-like syndrome. Treatment options are hormone replacement therapy, dietary intervention, or hematopoietic stem cell transplantation. Zellweger syndrome spectrum (ZSS) is a continuum of severe disorders affecting the nervous system, vision, hearing, and liver function. Most individuals present in infancy, but adult patients have been identified. The prevalence of ZSS is 1 in 50,000. ZSS follows autosomal recessive inheritance. At least 12 different genes have been implicated in ZSS, with approximately 60% to 70% of mutations occurring in PEX1. The clinical phenotypes include Zellweger syndrome, neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease (IRD). Individuals with Zellweger syndrome typically die within the first year of life without making any developmental progress. Individuals with NALD or IRD typically present in childhood with developmental delays, vision loss, hearing loss, and have a much slower disease progression. There is no specific treatment for ZSS. Although ZSS disorders are not a primary disease target for testing, this test will detect infants with these disorders.

**Useful For:** First-tier newborn screen for the lysosomal disorders: Fabry, Gaucher, Krabbe, mucopolysaccharidosis I (MPS-I), Niemann-Pick types A and B, and Pompe (Glycogen storage disorder type II) First-tier newborn screen for the peroxisomal disorder: X-linked adrenoleukodystrophy; may also detect Zellweger spectrum disorders

**Interpretation:** An interpretive report is provided. The quantitative measurements of informative metabolites and related ratios and their bioinformatic evaluation using the Collaborative Laboratory Integrated Reports (CLIR) system support the initial interpretation of the complete profile and may suggest the need to perform the measurement of more specific biomarkers using the original newborn screen specimen (second-tier test). Nevertheless, abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis, independent biochemical (ie, in vitro enzyme assay) or molecular genetic analyses are required, many of which are offered within Mayo Clinic’s Division of Laboratory Genetics and Genomics. The reports are in text form only. In a case with a completely normal profile, where the interpretation is reported as negative for all of the listed groups of conditions, no values are provided. A report for an abnormal screening result includes a quantitative result for the relevant abnormal biomarkers including those of a second-tier test when applicable, the CLIR score indicating the similarity of the newborn’s results to those derived from known patients with the relevant disease, a detailed interpretation of the results, and recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis).

**Reference Values:**
Not applicable

**Clinical References:**
Lysosomal and Peroxisomal Storage Disorders Screen, Blood Spot

Clinical Information: Lysosomes are intracellular organelles that contain hydrolytic enzymes to degrade a variety of macromolecules. Lysosomal storage disorders are a diverse group of inherited diseases where macromolecules accumulate due to defects in their transport mechanisms across the lysosomal membrane or due to defective lysosomal enzyme function. Accumulation of these macromolecules in the lysosomes leads to cell damage and, eventually, organ dysfunction. More than 40 lysosomal storage disorders have been described with a wide phenotypic spectrum. Gaucher disease is an autosomal recessive lysosomal storage disorder caused by a deficiency of acid beta-glucosidase (glucocerebrosidase: GBA) resulting in increased storage of glucocerebroside (D-glucosylceramide). The deposition of glucocerebroside in macrophages of the reticuloendothelial system (Gaucher cells) causes organ dysfunction and organomegaly. Gaucher cells, found in the spleen, bone marrow, lung, lymph nodes, and liver, are characteristic of the disease. There are 3 clinical types of Gaucher disease: Type I: adult/chronic -Type II: acute neuropathic/infantile -Type III: subacute neuropathic/juvenile Type I, the most frequent form of the disease, is characterized by organomegaly, thrombocytopenia, and bone pain, and is frequent among the Ashkenazim. Hepatosplenomegaly is usually present in all 3 types. Involvement of the central nervous system (CNS) is limited to the infantile type (type II). Enzyme replacement therapy and/or substrate reduction therapy are available for patients with Gaucher disease type I. Niemann-Pick disease types A and B are caused by a deficiency of sphingomyelinase which results in extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and, to a lesser degree, brain. Niemann-Pick type A disease is more severe than type B and characterized by early onset with feeding problems, dystrophy, persistent jaundice, development of hepatosplenomegaly, neurological deterioration, deafness, and blindness leading to death by age 3. Niemann-Pick type B disease is limited to visceral symptoms with survival into adulthood. Some patients have been described with intermediary phenotypes. Characteristic of the disease are large lipid-laden foam cells. Approximately 50% of cases have cherry-red spots in the macula. Sphingomyelinase is encoded by the SMPD1 gene. Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA; acid maltase) due to mutations in the GAA gene. The estimated incidence is 1 in 40,000 live births. In Pompe disease, glycogen that is taken up by lysosomes during physiologic cell turnover accumulates, causing lysosomal swelling, cell damage, and, eventually, organ dysfunction. This leads to progressive muscle weakness, cardiomyopathy, and, ultimately, death. The clinical phenotype appears to be dependent on residual enzyme activity. Complete loss of enzyme activity causes onset in infancy leading to death, typically within the first year of life. Juvenile and adult-onset forms are characterized by later onset and longer survival with primary symptoms that include muscle weakness and respiratory insufficiency, though rarely, clinically significant cardiomyopathy can be seen. Since Pompe disease is considered a rare condition that progresses rapidly in infancy, the disease, when presenting as juvenile and adult-onset forms, is often diagnosed late, if at all, during the evaluation of patients presenting with muscle hypotonia, weakness, or cardiomyopathy. Treatment with enzyme replacement therapy is available and improves prognosis, making early diagnosis of Pompe disease desirable. Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by a deficiency of galactocerebrosidase (GALC, galactosylceramide beta-galactosidase). Galactosylceramide (as with sulfated galactosylceramide) is a lipid component of myelin. The absence of GALC results in globular, distended, multinucleated bodies in the basal ganglia, pontine nuclei, and cerebral white matter. There is
severe demyelination throughout the brain with progressive cerebral degenerative disease affecting primarily the white matter. Severely affected individuals typically present between 3 to 6 months of age with increasing irritability and sensitivity to stimuli. Rapid neurodegeneration including white matter disease follows with death usually occurring by age 2. A subset of individuals has later onset forms of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression. They can present anywhere from age 6 months to the seventh decade of life, and based on newborn screening experience in New York, appear to be more common than the earlier onset variants. The clinical course of Krabbe disease can be variable, even within the same family. Of note, Krabbe disease variants, including pseudodeficiency, are not distinguishable by enzyme activity measurement. Hematopoietic stem cell transplantation, particularly when performed within the first few weeks of life, is a treatment option with potential benefit. Fabry disease is an X-linked recessive disorder with an incidence of approximately 1 in 50,000 males. Symptoms result from a deficiency of the enzyme alpha-galactosidase A (GLA; ceramide trihexosidase). Reduced GLA activity results in accumulation of glycosphingolipids in the lysosomes of both peripheral and visceral tissues. Severity and onset of symptoms are dependent on the residual GLA activity. Males with less than 1% GLA activity have the classic form of Fabry disease. Symptoms can appear in childhood or adolescence and usually include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, and corneal opacity. Renal insufficiency, leading to end-stage renal disease and cardiac and cerebrovascular disease, generally occurs in middle age. Males with residual α-Gal A activity greater than 1% may present with one of 3 variant forms of Fabry disease with onset of symptoms later in life: a renal variant associated with end-stage renal disease (ESRD) but without the pain or skin lesions, a cardiac variant typically presenting in the sixth to eighth decade with left ventricular hypertrophy, cardiomyopathy and arrhythmia, and proteinuria, but without ESRD, and a cerebrovascular variant presenting as stroke or transient ischemic attack. The variant forms of Fabry disease may be underdiagnosed. Females who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. Enzyme replacement therapy is a treatment option for Fabry disease. Mucopolysaccharidosis I (MPS I) is an autosomal recessive disorder caused by a reduced or absent activity of the alpha-L-iduronidase enzyme. Deficiency of the alpha-L-iduronidase enzyme can result in a wide range of phenotypes further categorized into 3 syndromes: Hurler syndrome (MPS IH), Scheie syndrome (MPS IS), and Hurler-Scheie syndrome (MPS IH/S). Because there is no way to distinguish the syndromes biochemically, they are also referred to as MPS I and attenuated MPS I. Clinical features and severity of symptoms of MPS I are widely variable, ranging from severe disease to an attenuated form that generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, progressive dysostosis multiplex, hepatosplenomegaly, corneal clouding, hearing loss, mental retardation or learning difficulties, and cardiac valvular disease. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. Peroxisomal disorders include 2 major subgroups: disorders of peroxisomal biogenesis and single peroxisomal enzyme/transporter defects. Peroxisomes are organelles present in all human cells except mature erythrocytes. They carry out essential metabolic functions including beta-oxidation of very long-chain fatty acids (VLCA), alpha-oxidation of phytanic acid, and biosynthesis of plasmalogen and bile acids. Peroxisome biogenesis defects such as Zellweger spectrum disorders are characterized by defective assembly of the entire organelle, whereas in single enzyme/transporter defects such as X-linked adrenoleukodystrophy, the organelle is intact, but a specific function is disrupted. These disorders are clinically diverse and range in severity from neonatal lethal to milder, later onset variants. Zellweger syndrome spectrum (ZSS) is a continuum of severe disorders affecting the nervous system, vision, hearing, and liver function. Most individuals present in infancy, but adult patients have been identified. The prevalence of ZSS is 1 in 50,000. ZSS follows autosomal recessive inheritance. At least 12 different genes have been implicated in ZSS, with approximately 60% to 70% of mutations occurring in PEX1. The clinical phenotypes include Zellweger syndrome, neonatal adrenoleukodystrophy (NALD), and infantile Refsum disease (IRD). Individuals with Zellweger syndrome typically die within the first year of life without making any developmental progress. Individuals with NALD or IRD typically present in childhood with developmental delays, vision loss, and hearing loss, and have a much slower disease progression. There is no specific treatment for ZSS. X-linked adrenoleukodystrophy (XALD) is a disorder affecting the nervous system, adrenal cortex, and testis. It is the most common of the peroxisomal disorders, affecting 1 in 17,000 to 1 in 21,000 males. A defect in the ABCD1 gene is responsible for the disease. X-ALD shows a wide range of phenotypic expressions. The clinical phenotypes occurring in males can be subdivided in 4 main categories: cerebral inflammatory, adrenomyeloneuropathy (AMN), Addison only, and asymptomatic.
phenotypes account for almost 80% of the patients, while the frequency of the asymptomatic category diminishes with age and it is very rare after age 40. It is estimated that approximately 50% of heterozygotes are symptomatic and develop an AMN-like syndrome. Treatment options are hormone replacement therapy, dietary intervention, or hematopoietic stem cell transplantation.

**Useful For:** Evaluation of patients with a clinical presentation suggestive of a lysosomal storage disorder, specifically Gaucher, Niemann-Pick type A or type B, Pompe, Krabbe, Fabry disease, or mucopolysaccharidosis I; or a peroxisomal disorder, either X-linked adrenoleukodystrophy or Zellweger syndrome spectrum.

**Interpretation:** An interpretive report is provided. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies at Mayo Medical Laboratories or elsewhere, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on the analysis, independent biochemical (eg, in vitro enzyme assay) or molecular genetic analyses are required.

**Reference Values:**

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**Clinical References:**

**LSDP 64908**

**Lysosomal Storage Disease Panel by Next-Generation Sequencing**

**Clinical Information:** Lysosomal storage diseases (LSDs) encompass a group of over 40 inherited biochemical diseases in which genetic mutations cause defective lysosomal functioning. Lysosomes perform catabolic functions for cells, which is accomplished through activity of various proteins such as
lysosomal enzymes, transport proteins, and other proteins. Functional deficits in these proteins cause an accumulation of substrates in cells leading to progressive organ dysfunction. This leads to variable clinical features that can affect the cardiovascular, neurological, ocular, and skeletal systems, among others. Clinical features are dependent on the amount and location of the substrate accumulation, but may include the following: characteristic facial features (coarse features), hepatomegaly, deafness, vision loss, abnormal skeletal findings, hydrops fetalis, ataxia, hypotonia, developmental delay/regression, and intellectual disability. Age of onset is variable, with symptoms presenting from the prenatal period to adulthood, but generally LSDs are progressive and cause significant morbidity and mortality with a decreased lifespan. Enzyme replacement therapy and oral substrate inhibitors are therapeutic options for some LSDs. LSDs are inherited in an autosomal recessive manner with the exception of Hunter, Fabry, and Danon diseases, which are X-linked. There are some founder mutations associated with particular LSDs in the Ashkenazi Jewish and Finnish populations, leading to an increased carrier frequency for some. Overall, the prevalence of LSDs is estimated at 1/7000 to 1/8000. Neuronal ceroid lipofuscinoses (NCLs) are a subset of lysosomal storage diseases that involve defective cellular processing of lipids. NCLs are clinically characterized by epilepsy, intellectual and motor decline, and blindness. Electron microscopy typically shows a characteristic accumulation of granular osmophic deposits (GROD), curvilinear profiles (CVB), or fingerprint profiles (FP). Enzymatic testing may show deficiency in palmitoyl-protein thioesterase 1 (PPT1), tripeptidyl-peptidase 1 (TPP1), or cathepsin D (CTSD). Currently there are at least 14 genetically distinct forms. Age of onset and clinical features can be variable, from congenital to adult onset. NCL is typically inherited in an autosomal recessive manner, although one adult onset form (ANCL; DNAJC5 gene) has been shown to be autosomal dominant. First-tier biochemical testing is available for the 2 most common types of enzyme deficiency resulting in NCL: TPPTL / Tripeptidyl Peptidase 1 (TPP1) and Palmitoyl-Protein Thioesterase 1 (PPT1), Leukocytes; and TPPTF / Tripeptidyl Peptidase 1 (TPP1) and Palmitoyl-Protein Thioesterase 1 (PPT1), Fibroblasts. This panel includes sequencing of 43 genes related to various LSDs, as well as 15 genes specific to neuronal ceroid lipofuscinosis genes is also available separately, see NCLP / Neuronal Cereoid Lipofuscinosis (NCL, Batten Disease) Panel by Next-Generation Sequencing. Gene Disease Name OMIM ID Inheritance ACP2 Lysosomal acid phosphatase deficiency (ACPHD) 200950 AR AGA Aspartylglucosaminuria (AGU) 208400 AR *Finnish Founder mutation ARSA Metachromatic leukodystrophy 250100 AR ARSB Muco polysaccharidosis Type VI maroteaux-lamy 253200 AR ARSH Multiple sulfatase deficiency 300586 AR ASAH1 Farber lipogranulomatosis 228000 AR CHIT1 Chitotriosidase deficiency (with Gaucher 1) 600031 614122 AR CTNS Cystinosis 219800 AR CTSA Galactosialidosis 256540 AR FUCA1 Fucosidosis 230000 AR GAA Pompe disease-glycogen storage disease type II 232300 AR GLA Fabry disease 301500 X linked GLB1 Mucopolysaccharidosis type IVB-MorquioB 253010 AR GM2A GM2-gangliosidosis, AB variant 272750 AR GNPTAB Mucolipidosis II, and III 252500 252600 AR GNPTG Mucolipidosis III gamma 232605 AR GNS Mucopolysaccharidosis type IIID Sanfilippo D 252940 AR GUSB Mucopolysaccharidosis type VII Sly 253220 AR HEXA Tay-Sachs disease 272800 AR HEX8 Sandhoff disease 268800 AR HGSNAT Mucopolysaccharidosis type IIIC (Sanfilippo) 252930 AR HYAL1 Mucopolysaccharidosis type IX: Hyaluronidase deficiency 601492 AR IDS Mucopolysaccharidosis type II Hunter disease 309900 AR IDUA Mucopolysaccharidosis type I (Hurler/Scheie) 607014 AR LAMC2 Glycosogen Storage Disease Type IIB-Danon Disease 300257 AR LIPA Lysosomal acid lipase deficiency/Wolman disease 278000 AR MAN2B1 Alpha-mannosidase deficiency 248500 AR MANBA Beta-mannosidosis 248510 AR MCOLN1 Mucolipidosis type IV 252650 AR NAGA Schindler disease 609241 AR NAGLU Mucopolysaccharidosis Type IIB 252920 AR NEU1 Sialidosis 256550 AR NPC1 Niemann-Pick type 1 and C2 257220 AR NPC2 Niemann-Pick type 1 and C3 607625 AR PSAP Prosaposin Deficiency (Variants of other disorders as well) 611721 610539 611722 249900 AR SGSH Mucopolysaccharidosis Type IIIA Sanfilippo 252900 AR SLC17A5 Sialic acid storage disease 269920 AR SMPD1 Niemann-Pick type A/B 257220 607616 AR SUMF1 Multiple Sulfatase Deficiency 272200 AR AR=autosomal recessive AD=autosomal dominant
**Useful For:** Follow up for abnormal biochemical results and confirmation of suspected lysosomal storage disease (LSD) Identifying mutations within genes known to be associated with LSD, allowing for predictive testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.


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**Lysosomal Storage Disorders Newborn Screen, Blood Spot**

**Clinical Information:** Lysosomes are intracellular organelles that contain hydrolytic enzymes that degrade a variety of macromolecules. Lysosomal storage disorders are a diverse group of inherited diseases characterized by the intracellular accumulation of macromolecules due to defects in their transport mechanisms across the lysosomal membrane or due to defective lysosomal enzyme function. The accumulation of these macromolecules leads to cell damage and, eventually, organ dysfunction. More than 40 lysosomal storage disorders have been described with a wide phenotypic spectrum. Gaucher disease is an autosomal recessive lysosomal storage disorder caused by a deficiency of the enzyme, beta-glucosidase. Beta-glucosidase facilitates the lysosomal degradation of glucosylceramide (glucocerebroside) and glucosylsphingosine (glucosylsphingosine). Gaucher disease is caused by mutations in the GBA gene. There are 3 described types of Gaucher disease with varying clinical presentations and age of onset from a perinatal lethal disorder to an asymptomatic type. Features of all types of Gaucher disease include hepatosplenomegaly and hematological abnormalities. Treatment is available in the form of enzyme replacement therapy, substrate reduction therapy, and chaperone therapy for types 1 and 3. Currently, only supportive therapy is available for type 2. Niemann-Pick types A and B are caused by a deficiency of sphingomyelinase due to mutations in the SMPD1 gene. The result is extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and, to a lesser degree, brain. Classification of type A versus type B is based on the age of onset as well as the severity of symptoms. Niemann-Pick type A disease is more severe and characterized by early onset with feeding problems, dystrophy, persistent jaundice, cherry red maculae, development of hepatosplenomegaly, neurological deterioration, deafness, and blindness, leading to death by age 3. Niemann-Pick type B disease is limited to visceral symptoms with survival into adulthood. Some patients have been described with intermediary phenotypes. Characteristic of the disease are large lipid-laden foam cells on bone marrow biopsy. The combined prevalence of the two types is estimated to be 1 in 250,000. Treatment is supportive, although there are clinical trials in place. Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA; acid maltase) due to mutations in the GAA gene. The estimated incidence is 1 in 40,000 live births. In Pompe disease, glycogen that is taken up by lysosomes during physiologic cell
turnover accumulates, causing lysosomal swelling, cell damage, and, eventually, organ dysfunction. The clinical presentation of Pompe disease ranges from a rapidly progressive infantile variant, which is uniformly lethal if untreated, to a more slowly progressive late-onset variant. All disease variants are eventually associated with progressive muscle weakness and respiratory insufficiency. Cardiomyopathy is associated almost exclusively with the infantile form. Enzyme replacement therapy is available for all variants and should be started as soon as possible for patients with the infantile variant and at the first signs of muscle weakness in the later onset variants. Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive disorder caused by mutations in the GALC gene resulting in a deficiency of galactocerebrosidase (GALC, galactosylceramide beta-galactosidase). Galactosylceramide (as with sulfated galactosylceramide) is a lipid component of myelin. The absence of GALC results in globular, distended, multinucleated bodies in the basal ganglia, pontine nuclei, and cerebral white matter. There is severe demyelination throughout the brain with progressive cerebral degenerative disease affecting primarily the white matter. Patients with this early infantile onset variant of Krabbe disease (<1 in 250,000 live births) die within 2 years. Late infantile-onset Krabbe disease manifests between 6 and 12 months of life and leads to death within a few years as well. Juvenile and adult onset variants present later in life, progress more slowly and, based on newborn screening experience in New York, appear to be more common than the earlier onset variants. Of note, Krabbe disease variants, including pseudodeficiency, may not be discriminated by enzyme activity measurement. Molecular genetic analysis of the GALC gene may provide information on expected age of first symptoms. Psychosine has been shown to be elevated in patients with clinical signs and symptoms of disease and therefore, may be a useful biomarker for the presence of disease or disease progression. The only available therapy is hematopoietic stem cell transplantation that is best performed prior to the onset of clinical symptoms. Early infantile Krabbe disease must therefore be considered a critical, time sensitive newborn screening condition. Fabry disease, caused by mutations in the GLA gene, is an X-linked recessive disorder with an incidence of approximately 1 in 50,000 males. Symptoms result from a deficiency of the enzyme alpha-galactosidase A (GLA; ceramide trihexosidase). Reduced GLA activity results in accumulation of glycosphingolipids in the lysosomes of both peripheral and visceral tissues. Severity and onset of symptoms are dependent on the residual GLA activity. Males with less than 1% GLA activity have the classic form of Fabry disease. Symptoms can appear in childhood or adolescence and usually include acroparesthesias (pain crises), multiple angiokeratomas, reduced or absent sweating, and corneal opacity. Renal insufficiency, leading to end-stage renal disease and cardiac and cerebrovascular disease, generally occur in middle age. Males with more than 1% GLA activity may present with a variant form of Fabry disease. The renal variant generally has onset of symptoms in the third decade. The most prominent feature in this form is renal insufficiency and, ultimately, end-stage renal disease. Individuals with the renal variant may or may not share other symptoms with the classic form of Fabry disease. Individuals with the cardiac variant are often asymptomatic until they present with cardiac findings such as cardiomyopathy or mitral insufficiency in the fourth decade. The cardiac variant is not associated with renal failure. Females who are carriers of Fabry disease can have clinical presentations ranging from asymptomatic to severely affected. Pseudodeficiency alleles may also be detected by newborn screening. Treatment with enzyme replacement therapy (ERT) is available for both males and females with Fabry disease. Mucopolysaccharidosis I (MPS-I) is an autosomal recessive disorder caused by a reduced or absent activity of the alpha-L-iduronidase (IDUA) enzyme. MPS-I is caused by mutations in the IDUA gene and has an estimated incidence of approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy.

**Useful For:** First-tier newborn screen for the lysosomal disorders: Fabry, Gaucher, Krabbe, mucopolysaccharidosis I (MPS-I), Niemann-Pick types A and B, and Pompe (Glycogen storage disorder type II)

**Interpretation:** An interpretive report is provided. The quantitative measurements of informative metabolites and related ratios and their bioinformatic evaluation using the Collaborative Laboratory Integrated Reports (CLIR) system support the initial interpretation of the complete profile and may suggest the need to perform the measurement of more specific biomarkers using the original newborn screen specimen (second-tier test). Nevertheless, abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis, independent biochemical (ie, in vitro enzyme assay) or molecular genetic analyses are required, many of which are offered within Mayo Clinic’s Division of Laboratory Genetics and Genomics. The reports are in text form only. In a case with a completely normal profile, where the interpretation is reported as negative for all of the listed
groups of conditions, no values are provided. A report for an abnormal screening result includes a quantitative result for the relevant abnormal biomarkers including those of a second-tier test when applicable, the CLIR score indicating the similarity of the newborn’s results to those derived from known patients with the relevant disease, a detailed interpretation of the results, and recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis).

**Reference Values:**
Not applicable

**Clinical References:**

**Lysosomal Storage Disorders Screen, Urine**

**Clinical Information:** Lysosomal storage disorders (LSD) are a diverse group of inherited diseases characterized by the intracellular accumulation of macromolecules leading to cell damage and organ dysfunction. Approximately 50 lysosomal storage disorders have been described with a wide phenotypic spectrum and ranging in severity from neonatal lethal to later onset milder variants. Although classification is not always straightforward, LSDs are generally categorized according to the type of storage material that accumulates in the cells and tissues. Major categories include mucopolysaccharidoses, oligosaccharidoses, mucolipidoses, and sphingolipidoses. In many cases, accumulating analytes can be detected in urine. Screening for these disorders typically begins with an analysis to detect disease-specific metabolite patterns or profiles indicative of a LSD. The combined analysis of disease-specific markers for LSDs in multiple tests can allow for the identification of additional disorders that may not be picked up using any of the single tests alone. Disorders detectable by this approach include the oligosaccharidoses alpha-mannosidosis, aspartylglucosaminuria, fucosidosis, Schindler disease, and sialidosis; the sphingolipidoses GM1 gangliosidosis, Sandhoff disease, galactosialidosis, saposin B deficiency, metachromatic leukodystrophy, multiple sulfatase deficiency, Fabry disease, Gaucher disease, and Krabbe disease; the mucopolysaccharidoses excluding MPS IX (hyaluronidase deficiency); the glycogen storage disorder Pompe disease and the mucolipidoses types II and III. Additionally, other disorders such as CDG type Ib, and de-glycosylation disorders such as NGLY1-CDG may also be detected. The mucopolysaccharidoses (MPS) are a subset of lysosomal storage disorders caused by the deficiency of any one of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAGs). Undegraded or partially degraded GAGs (also called mucopolysaccharides) are stored in lysosomes and excreted in the urine. Accumulation of GAGs in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in MPS disorders. There are 11 known enzyme deficiencies that result in MPS. In addition, abnormal GAG storage is observed in multiple sulfatase deficiency and in I-cell disease. Finally, an abnormal excretion of GAGs in urine is observed occasionally in other disorders including active bone diseases, connective tissue disease, hypothyroidism, urinary dysfunction, and oligosaccharidoses. The oligosaccharidoses (glycoproteinoses) are a subset of lysosomal storage disorders caused by the deficiency of any one of the lysosomal enzymes involved in the degradation of complex oligosaccharide chains. They are characterized by the abnormal accumulation of incompletely degraded oligosaccharides in cells and tissues and the corresponding increase of related free oligosaccharides in the urine. Clinical features can include bone abnormalities, coarse facial features, corneal cloudiness, organomegaly, muscle weakness, hypotonia, developmental delay, and ataxia. Age of onset ranges from early infancy to adult and can even present prenatally. The sphingolipidoses are a...
subset of lysosomal storage disorders caused by a defect in any one of the enzymes that degrade complex ceramide containing lipids. They are characterized by the excessive accumulation of sphingolipids in the tissues, particularly in the central nervous system resulting in progressive neurodegeneration and developmental regression. In 2 conditions, Fabry disease and Gaucher disease type I, there is only systemic involvement. In many cases, sphingolipidoses can be detected by through oligosaccharide analysis in urine. Because of the similarity of features across disorders and their variability, clinical diagnosis of LSDs can be challenging; therefore, urine screening and the combined analysis of multiple urine screening tests is an important tool for the initial workup of an individual suspected of having a lysosomal storage disorder. Abnormal results can be followed up with the appropriate enzyme or molecular analysis.

**Useful For:** Screening patients suspected of having a lysosomal storage disorder

**Interpretation:** Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. Follow-up testing is recommended to confirm a diagnosis. When abnormal results are detected with characteristic patterns, a detailed interpretation is given, including an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro confirmatory studies (enzyme assay and molecular test).

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**LYZZ**

**Lysozyme (LYZ) Gene, Full Gene Analysis**

**Clinical Information:** The systemic amyloidoses are a number of disorders of varying etiology characterized by extracellular protein deposition. The most common form is an acquired amyloidosis secondary to multiple myeloma or monoclonal gammopathy of unknown significance (MGUS) in which the amyloid is composed of immunoglobulin light chains. In addition to light chain amyloidosis, there are a number of acquired amyloidoses caused by the misfolding and precipitation of a wide variety of proteins. There are also hereditary forms of amyloidosis. The hereditary amyloidoses comprise a group of autosomal dominant, late-onset diseases that show variable penetrance. A number of genes have been associated with hereditary forms of amyloidosis, including those that encode transthyretin, apolipoprotein AI, apolipoprotein AII, fibrinogen alpha chain, gelsolin, cystatin C and lysozyme. Apolipoprotein AI, apolipoprotein AII, lysozyme, and fibrinogen amyloidosis present as non-neuropathic systemic amyloidosis, with renal dysfunction being the most prevalent manifestation. Lysozyme (LYZ) gene-related familial visceral amyloidosis presents clinically with significant renal impairment. The renal dysfunction occurs at an early age and, in the absence of treatment, results in renal failure. Other manifestations of LYZ-related familial visceral amyloidosis include gastrointestinal involvement, cardiac disease, Sicca syndrome, and propensity towards petechiae, hemorrhage and hematomata, including hepatic hemorrhage. The bleeding tendency associated with LYZ-related familial visceral amyloidosis has included rupture of abdominal lymph nodes. Neuropathy is not a feature of LYZ-related familial visceral amyloidosis. Due to the clinical overlap between the acquired and hereditary forms, it is imperative to determine the specific type of amyloidosis in order to provide an accurate prognosis and consider appropriate therapeutic interventions. Tissue-based, laser capture tandem mass spectrometry might serve as a useful test preceding gene sequencing to better characterize the etiology of the amyloidosis, particularly in cases that are not clear clinically.

**Useful For:** Confirming a diagnosis of lysozyme (LYZ) gene-related familial visceral amyloidosis

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LYZZ 35471

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  Page 1422
**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Lysozyme (Muramidase), Plasma**

**Clinical Information:** Lysozyme is a bacteriolytic enzyme that is found in some hematopoietic cells. It is primarily present in granulocytes, monocytes, and histiocytes. The enzyme is present in only minute amounts in lymphocytes; and is not present in myeloblasts, eosinophils, and basophils. Lysozyme in the plasma comes chiefly from the degradation of granulocytes and monocytes and its concentration reflects the turnover of these cells. Increases are seen in benign (eg, infection, inflammation) and malignant processes (eg, some leukemias). Plasma lysozyme is elevated in patients with acute or chronic granulocytic or monocytic leukemias and falls with successful treatment. Conversely, patients with lymphocytic leukemia may have depressed plasma lysozyme levels. Patients with renal disorders (including rejection of transplanted kidneys) or Crohn’s disease (regional enteritis) also tend to have elevated levels of plasma lysozyme.

**Useful For:** Confirming marked increases in the granulocyte or monocyte pools as in granulocytic or monocytic leukemias, myeloproliferative disorders, and malignant histiocytosis Following the course of therapy in cases of chronic granulocytic or chronic monocytic leukemias

**Interpretation:** Levels >200 mcg/mL may be seen in acute nonlymphocytic leukemia (M2, M4, M5) or chronic granulocytic leukemias.

**Reference Values:**
> or =12 months: 2.7-9.4 mcg/mL

Reference values have not been established for patients who are <12 months of age.


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**Lysozyme Immunostain, Technical Component Only**

**Clinical Information:** Lysozyme is an intracellular enzyme found in the primary granules of myeloid cells, monocytes, and histiocytes. Diagnostically, antibodies to lysozyme can help confirm monocytic and histiocytic differentiation in acute myeloid leukemia or histiocytic sarcoma.

**Useful For:** Aids in confirmation of monocytic and histiocytic differentiation

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and
negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Lysozyme, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
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<tbody>
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<td>0</td>
<td></td>
<td>Negative</td>
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<tr>
<td>1</td>
<td>0.35-0.69</td>
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<tr>
<td>2</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**Clinical References:** Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and Management by Laboratory Methods. 21st edition. Edited by RA McPherson, MR Pincus. WB Saunders
FLYSO 58101

**Lysozyme, Serum**

**Clinical Information:** Serum lysozyme levels may be elevated in acute myelomonocytic leukemia (FAB-M4), chronic myelomonocytic leukemia (CMML), and chronic myelocytic leukemia (CML). Increased serum lysozyme activity is present in tuberculosis, sarcoidosis, megaloblastic anemias, acute bacterial infections, ulcerative colitis, regional enteritis, and Crohn disease. Elevated serum lysozyme occurs during severe renal insufficiency, renal transplant rejection, urinary tract infections, pyelonephritis, glomerulonephritis, and nephrosis.

**Reference Values:**
0.00 - 2.75 ug/mL

MPTS 65198

**M-Protein Isotype by Matrix-Assisted Laser Desorption/Ionization-Time of Flight Mass Spectrometry (MALDI-TOF MS), Serum**

**Clinical Information:** Immunotyping of monoclonal (M-) proteins identifies the monoclonal immunoglobulin heavy chain type (gamma, alpha, mu, delta, or epsilon) and light chain type (kappa or lambda) in serum specimens.

**Useful For:** Aiding in the diagnosis of monoclonal gammopathies, when used in conjunction with free light chain studies

**Interpretation:** A characteristic monoclonal band (M-spike) is often found on serum protein electrophoresis (SPE) in the gamma globulin region and, more rarely, in the beta or alpha-2 regions. The finding of an M-spike, restricted migration, or hypogammaglobulinemic protein electrophoresis pattern is suggestive of a possible monoclonal protein. Immunoaffinity purification followed by matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) is performed to identify the immunoglobulin heavy and light chains.

**Reference Values:**
Only orderable as part of a profile. For more information see:
- SPISO / Protein Electrophoresis and Isotype, Serum
- SMOGA / Monoclonal Gammopathy Screen, Serum
- MMOGA / Monoclonal Gammopathy Monitor, Serum

No monoclonal protein detected


MACNT 65405

**Macadamia Nut, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic diseases, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children under 5 years due to food sensitivity (milk, egg, soy, and wheat
proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens that may be responsible for allergic disease or an anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**MACE 82492**

**Mace, IgE**

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<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt;100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Mackerel, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Macroamylase

Reference Values: Not Detected

Macroprolactin, Serum

Clinical Information: Prolactin is secreted by the anterior pituitary gland under negative control by dopamine, which is secreted by the hypothalamus. The only physiological function of prolactin is the stimulation of milk production. In normal individuals, the prolactin concentration in blood rises in response to physiologic stimuli such as nipple stimulation, sleep, exercise, sexual intercourse, and hypoglycemia. Certain medications, (eg, phenothiazines, metoclopramide, risperidone, selective serotonin reuptake inhibitors, estrogens, verapamil) may also cause hyperprolactinemia. Pathologic causes of hyperprolactinemia include prolactin-secreting pituitary adenoma (prolactinaoma), diseases of the hypothalamus, primary hypothyroidism, section compression of the pituitary stalk, chest wall lesions, renal failure, and ectopic tumors. Hyperprolactinemia may also be caused by the presence of a high-molecular-mass complex of prolactin called macroprolactin (typically due to prolactin bound to immunoglobulin). In this situation, the patient is asymptomatic. Hyperprolactinemia attributable to macroprolactin is a frequent cause of misdiagnosis and mismanagement of patients. Macroprolactin should be considered if, in the presence of elevated prolactin levels, signs and symptoms of hyperprolactinemia are absent, or pituitary imaging studies are not informative.

Useful For: Determining biologically active levels of prolactin, in asymptomatic patients with elevated prolactin levels Ruling out the presence of macroprolactin

Interpretation: When the fraction (percentage) of polyethylene glycol (PEG)-precipitated (complexed) prolactin is 60% or less of total prolactin, the specimen is considered negative for macroprolactin. When total prolactin exceeds the upper reference limit and macroprolactin is negative, other causes for hyperprolactinemia should be explored. When the fraction (percentage) of polyethylene glycol (PEG)-precipitated (complexed) prolactin is above 60%, the specimen is considered positive for the presence of macroprolactin. Following polyethylene glycol (PEG)-precipitation, a patient whose unprecipitated prolactin concentration is greater than the upper limit of the unprecipitated prolactin reference interval may have hyperprolactinemia. See PRL / Prolactin, Serum for interpretation of prolactin levels.

Reference Values:
PROLACTIN, TOTAL
Males
<18 years: not established
> or =18 years: 4.0-15.2 ng/mL
Females
<18 years: not established
> or =18 years: 4.8-23.3 ng/mL

PROLACTIN, UNPRECIPITATED
Males
<18 years: not established
> or =18 years: 2.7-13.1 ng/mL

Current as of October 11, 2018 2:20 pm CDT   800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Females
<18 years: not established
≥18 years: 3.4-18.5 ng/mL

When the percent of the precipitated (complexed) prolactin fraction of the total prolactin is 60% or less, the result is considered negative for macroprolactin.


**Magnesium, 24 Hour, Urine**

**Clinical Information:** Magnesium, along with potassium, is a major intracellular cation. Magnesium is a cofactor of many enzyme systems. All adenosine triphosphate-dependent enzymatic reactions require magnesium as a cofactor. Approximately 70% of magnesium ions are stored in bone. The remainder is involved in intermediary metabolic processes; about 70% is present in free form, while the other 30% is bound to proteins (especially albumin), citrates, phosphate, and other complex formers. The serum magnesium level is kept constant within very narrow limits. Renal handling of magnesium is determined by the combination of filtration and reabsorption. Roughly 70% of the magnesium in plasma is filtered by the glomeruli; 20% to 30% of the filtered magnesium is reabsorbed in the proximal tubule, while less than 5% is reabsorbed in the distal tubule and collecting duct.

Numerous causes of renal magnesium wasting have been identified including (but not limited to) congenital defects (including Barter and Gitelman syndrome), various endocrine disorders (including hyperaldosteronism and hyperparathyroidism), exposure to certain drugs (ie, diuretics, cis-platinum, aminoglycoside antibiotics, calcineurin inhibitors), and other miscellaneous causes (including chronic alcohol abuse). Gastrointestinal conditions associated with fat malabsorption and chronic diarrhea can cause fecal magnesium loss and hypomagnesemia. High levels of plasma magnesium are typically only seen in patients with decreased renal function, after administration of a magnesium load large enough to exceed the kidneys’ ability to excrete it, or a combination of the 2. Magnesium is an inhibitor of calcium crystal growth, and contributes to urinary calcium oxalate and calcium phosphate supersaturation. However, low urinary magnesium in isolation has not been identified as a common cause of kidney stones, nor has magnesium supplementation been proven as an effective therapy for stone prevention.

**Useful For:** Assessing the cause of abnormal serum magnesium concentrations Determining whether nutritional magnesium loads are adequate Calculating urinary calcium oxalate and calcium phosphate supersaturation and assessing kidney stone risk

**Interpretation:** Urinary magnesium excretion should be interpreted in concert with serum concentrations. In the presence of hypomagnesemia, a 24-hour urine magnesium >24 mg/day or fractional excretion >0.5% suggests renal magnesium wasting. Lower values suggest inadequate magnesium intake and/or gastrointestinal losses. In the presence of hypermagnesemia, urinary magnesium levels provide an indication of current magnesium intake. Lower urinary magnesium excretion increases urinary calcium oxalate and calcium phosphate supersaturation and could contribute to kidney stone risk.

**Reference Values:**
51-269 mg/24 hr

Reference values have not been established for patients <18 years and >83 years of age.
Reference values apply to 24-hour collections.

Reference Values:
Only orderable as part of a profile. For more information see SSATR / Supersaturation Profile, Pediatric, Random, Urine.

Magnesium, Random, Urine

Clinical Information: Magnesium, along with potassium, is a major intracellular cation. Magnesium is a cofactor of many enzyme systems. All adenosine triphosphate-dependent enzymatic reactions require magnesium as a cofactor. Approximately 70% of magnesium ions are stored in bone. The remainder is involved in intermediary metabolic processes; about 70% is present in free form, while the other 30% is bound to proteins (especially albumin), citrates, phosphate, and other complex formers. The serum magnesium level is kept constant within very narrow limits. Renal handling of magnesium is determined by the combination of filtration and reabsorption. Roughly 70% of the magnesium in plasma is filtered by the glomeruli; 20% to 30% of the filtered magnesium is reabsorbed in the proximal tubule, while less than 5% is reabsorbed in the distal tubule and collecting duct.(1) Numerous causes of renal magnesium wasting have been identified including (but not limited to) congenital defects (including Barter and Gitelman syndrome), various endocrine disorders (including hyperaldosteronism and hyperparathyroidism), exposure to certain drugs (ie, diuretics, cis-platinum, aminoglycoside antibiotics, calcineurin inhibitors), and other miscellaneous causes (including chronic alcohol abuse). Gastrointestinal conditions associated with fat malabsorption and chronic diarrhea can cause fecal magnesium loss and hypomagnesemia. High levels of plasma magnesium are typically only seen in patients with decreased renal function, after administration of a magnesium load large enough to exceed the kidneys’ ability to excrete it, or a combination of the two.(2) Magnesium is an inhibitor of calcium crystal growth, and contributes to urinary calcium oxalate and calcium phosphate supersaturation. However, low urinary magnesium in isolation has not been identified as a common cause of kidney stones, nor has magnesium supplementation been proven as an effective therapy for stone prevention.

Useful For: Assessing the cause of abnormal serum magnesium concentrations Determining whether nutritional magnesium loads are adequate Calculating urinary calcium oxalate and calcium phosphate supersaturation and assessing kidney stone risk.

Interpretation: Urinary magnesium excretion should be interpreted in concert with serum concentrations. In the presence of hypomagnesemia, a 24-hour urine magnesium >24 mg/day or fractional excretion >0.5% suggests renal magnesium wasting. Lower values suggest inadequate magnesium intake and/or gastrointestinal losses. In the presence of hypermagnesemia, urinary magnesium levels provide an indication of current magnesium intake. Lower urinary magnesium excretion increases urinary calcium oxalate and calcium phosphate supersaturation and could contribute to kidney stone risk.

Reference Values:
Random Magnesium/Creatinine Ratio: > or =0.035 mg/mg

Reference values have not been established for patients <18 years and >83 years of age.


Magnesium, Red Blood Cell

Reference Values:
3.5 - 7.1 mg/dL

Magnesium, Serum

Clinical Information: Magnesium, along with potassium, is a major intracellular cation. Magnesium is a cofactor of many enzyme systems. All adenosine triphosphate (ATP)-dependent enzymatic reactions
require magnesium as a cofactor. Approximately 70% of magnesium ions are stored in bone. The remainder is involved in intermediary metabolic processes; about 70% is present in free form while the other 30% is bound to proteins (especially albumin), citrates, phosphate, and other complex formers. The serum magnesium level is kept constant within very narrow limits. Regulation takes place mainly via the kidneys, primarily via the ascending loop of Henle. Conditions that interfere with glomerular filtration result in retention of magnesium and, hence, elevation of serum concentrations. Hypermagnesemia is found in acute and chronic renal failure, magnesium overload, and magnesium release from the intracellular space. Mild-to-moderate hypermagnesemia may prolong atrioventricular conduction time.

Magnesium toxicity may result in central nervous system (CNS) depression, cardiac arrest, and respiratory arrest. Numerous studies have shown a correlation between magnesium deficiency and changes in calcium, potassium, and phosphate homeostasis, which are associated with cardiac disorders such as ventricular arrhythmias that cannot be treated by conventional therapy, increased sensitivity to digoxin, coronary artery spasms, and sudden death. Additional concurrent symptoms include neuromuscular and neuropsychiatric disorders. Conditions that have been associated with hypomagnesemia include chronic alcoholism, childhood malnutrition, lactation, malabsorption, acute pancreatitis, hypothyroidism, chronic glomerulonephritis, aldosteronism, and prolonged intravenous feeding.

**Useful For:** Monitoring preeclampsia patients being treated with magnesium sulfate, although in most cases monitoring clinical signs (respiratory rate and deep tendon reflexes) is adequate and blood magnesium levels are not required.

**Interpretation:** Symptoms of magnesium deficiency do not typically appear until levels are 1.0 mg/dL or lower. Levels of 9.0 mg/dL or higher may be life-threatening.

**Reference Values:**
- 0-2 years: 1.6-2.7 mg/dL
- 3-5 years: 1.6-2.6 mg/dL
- 6-8 years: 1.6-2.5 mg/dL
- 9-11 years: 1.6-2.4 mg/dL
- 12-17 years: 1.6-2.3 mg/dL
- >17 years: 1.7-2.3 mg/dL

interpretation is performed). If diagnostic consultation by a pathologist is required order PATHC / Pathology Consultation. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Malaria PCR with Parasitemia Reflex

Clinical Information: Malaria is a major tropical disease infecting approximately 500 million people and causing 1.5 to 2.7 million deaths annually. Ninety percent of the deaths occur in sub-Saharan Africa and most of these occur in children <5 years old; it is the leading cause of mortality in this age group. This disease is also widespread in Central and South America, Hispaniola, the Indian subcontinent, the Middle East, Oceania, and Southeast Asia. In the United States, individuals at risk include travelers to and visitors from endemic areas. Malaria is caused primarily by 4 species of the protozoa Plasmodium: Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, and Plasmodium ovale. A fifth Plasmodium species, Plasmodium knowlesi, is a similar parasite that may be an important source of human infection in some regions of Southeast Asia. Differentiating Plasmodium falciparum and Plasmodium knowlesi from other species is important since both can cause life-threatening infections. In addition, Plasmodium falciparum is typically resistant to many commonly used antimalarial agents such as chloroquine. Microscopy of Giemsa-stained thick and thin blood films is the standard laboratory method for diagnosis and speciation of malaria parasites. Under optimal conditions, the sensitivity of the thick film microscopy is estimated to be 10 to 30 parasites per microliter of blood. However, microscopic diagnosis requires considerable expertise and may be insensitive or nonspecific when inadequate training and facilities are available. Furthermore, prolonged exposure to EDTA, transportation conditions, and prior use of antimalarial drugs may alter parasite morphology and negatively impact the ability to perform speciation by microscopy. Finally, Babesia parasites have a similar appearance to Plasmodium falciparum ring forms (early trophozoites) on peripheral blood films, resulting in potential diagnostic confusion. PCR is an alternative method of malaria diagnosis that allows for sensitive and specific detection of Plasmodium species DNA from peripheral blood. PCR may be more sensitive than conventional microscopy in very low parasitemias, and is more specific for species identification. It may be particularly useful when subjective microscopy does not permit certain identification of the species present. Malaria PCR can be used in conjunction with a traditional blood film or Babesia PCR when the clinical or morphologic differential includes both babesiosis and malaria. Examination of the thin film also allows for calculation of percent parasitemia, which can be used to predict prognosis and monitor response to treatment.

Useful For: Detection of Plasmodium DNA and identification of the infecting species An adjunct to conventional microscopy of Giemsa-stained films Detection and confirmatory identification of Plasmodium species: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, and Plasmodium knowlesi

Interpretation: A positive result indicates the presence of Plasmodium nucleic acid and melting curve analysis indicates the infecting species. When the malaria PCR is positive, the blood films will be examined so that the percentage of parasitemia can be calculated. The percentage of parasitemia will follow under reflex test ID PARCT.

Reference Values:
Negative
If positive, percent parasitemia will be calculated and reported.
Malaria Percent Parasitemia

**Clinical Information:** Malaria is a potentially life-threatening disease infecting approximately 500 million people and causing 1.5 to 2.7 million deaths annually. It is widespread in sub-Saharan Africa, Central and South America, Hispaniola, the Indian subcontinent, the Middle East, Oceania, and Southeast Asia. In the United States, individuals at risk include travelers and visitors from endemic areas. Examination of the thin film allows for calculation of percent parasitemia, which can be used to predict prognosis and monitor response to treatment for patients with malaria and babesiosis. The degree of parasitemia may change rapidly due to natural parasite replication and administration of antimalarial therapies. Therefore, the percent parasitemia should be calculated upon initial diagnosis and then monitored over time with treatment.

**Useful For:** Only orderable as a reflex. For more information see LMALP / Malaria PCR with Parasitemia Reflex. Calculation of percent parasitemia that can be used to predict prognosis and monitor response to treatment for patients with malaria and babesiosis

**Interpretation:** The percentage parasitemia represents the percentage of infected red blood cells. This is calculated from representative microscopic fields on the thin blood film. Gametocytes are not included in the calculation since they are not infectious to humans and are not killed by most antimalaria drugs.

**Reference Values:**

A percent parasitemia is provided following a positive result for Malaria PCR with Parasitemia Reflex.

Malaria, Molecular Detection, PCR Only

**Clinical Information:** Malaria is a major tropical disease infecting approximately 500 million people and causing 1.5 to 2.7 million deaths annually. Ninety percent of the deaths occur in sub-Saharan Africa and most of these occur in children <5 years old; it is the leading cause of mortality in this age group. This disease is also widespread in Central and South America, Hispaniola, the Indian subcontinent, the Middle East, Oceania, and Southeast Asia. In the United States, individuals at risk include travelers to and visitors from endemic areas. Malaria is caused primarily by 4 species of the protozoa Plasmodium: Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, and Plasmodium ovale. A fifth Plasmodium species, Plasmodium knowlesi, is a similar parasite that may be an important source of human infection in some regions of Southeast Asia. Differentiating Plasmodium falciparum and Plasmodium knowlesi from other species is important since both can cause life-threatening infections. In addition, Plasmodium falciparum is typically resistant to many commonly used antimalarial agents such as chloroquine. Microscopy of Giemsa-stained thick and thin blood films is the standard laboratory method for diagnosis and differentiation of malaria parasites. Under optimal conditions, the sensitivity of the thick film microscopy is estimated to be 10 to 30 parasites per microliter of blood. However, microscopic diagnosis requires considerable expertise and may be insensitive or nonspecific when inadequate training and facilities are available. Furthermore, prolonged exposure to EDTA, transportation conditions, and prior use of antimalarial drugs may alter parasite morphology and negatively impact the ability to perform species identification by microscopy. Finally, Babesia parasites have a similar appearance to Plasmodium falciparum ring forms (early trophozoites) on peripheral blood films, resulting in potential diagnostic confusion. PCR is an alternative method of malaria diagnosis that allows for sensitive and specific detection of Plasmodium species DNA from...
peripheral blood. PCR may be more sensitive than conventional microscopy in very low parasitemias, and is more specific for species identification. It may be particularly useful when subjective microscopy does not permit certain identification of the species present. Malaria PCR can be used in conjunction with a traditional blood film or Babesia PCR when the clinical or morphologic differential includes both babesiosis and malaria. Examination of the thin film also allows for calculation of percent parasitemia, which can be used to predict prognosis and monitor response to treatment. This test does not include blood smear examination or calculation of parasitemia.

**Useful For:** Detection of Plasmodium DNA and identification of the infecting species An adjunct to conventional microscopy of Giemsa-stained films, particularly in cases of low percent parasitemia or suboptimal parasite morphology Detection and confirmatory identification of Plasmodium species: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, and Plasmodium knowlesi

**Interpretation:** A positive result indicates the presence of Plasmodium nucleic acid and melting curve analysis indicates the infecting species.

**Reference Values:**

Negative

**Clinical References:**

**MAAN 82396 Maleic Anhydride, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com

MCMF 113355

Malignant Cells Cyto/Heme (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

MALT 82834

Malt, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children < 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com

MAML2 (11q21) Rearrangement, Mucoepidermoid Carcinoma (MEC), FISH, Tissue

Clinical Information: Mucoepidermoid carcinoma (MEC) is the most common malignant salivary gland neoplasm, representing over 30% of all malignant salivary gland tumors. The diagnosis of MEC can be quite challenging due to the degree of histologic overlap with other glandular, clear cell, or oncocytic salivary gland tumors. MAML2 rearrangements are detectable in 80% to 85% of MEC, but not in morphologic mimics such as oncocytic cystadenoma, Warthin tumor, oncocytoma, oncocytic carcinoma, acinic cell carcinoma, and metastatic renal cell carcinoma.

Useful For: Supporting a diagnosis of mucoepidermoid carcinoma

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the MAML2 probe. A positive result is consistent with a diagnosis of mucoepidermoid carcinoma (MEC). A negative result suggests no rearrangement of the MAML2 gene region at 11q21. However, this result does not exclude the diagnosis of MEC.

Reference Values:
An interpretive report will be provided.


Mammaglobin (MGB) Immunostain, Technical Component Only

Clinical Information: Mammaglobin, a mammary specific member of the uteroglobin family, is known to be overexpressed in human breast cancer. It may be valuable when used in a panel with GCDFP-15 and ER to evaluate tumors of unknown primary site.

Useful For: Breast-specific marker Aids in evaluating tumors of unknown primary site

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**MAND 82352**

**Mandarin, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>&gt; or =100</td>
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</tr>
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**MNU 8080**

**Manganese, 24 Hour, Urine**

**Clinical Information:** Manganese (Mn) is an essential trace element with many industrial uses. Manganese is the 12th most abundant element in the earth's crust and is used predominantly in the production of steel. These industrial processes cause elevated environmental exposures to airborne manganese dust and fumes, which in turn have led to well-documented cases of neurotoxicity among exposed workers. Mining and iron and steel production have been implicated as sources of exposure. Inhalation is the primary source of entry for manganese toxicity. Signs of toxicity may appear quickly or not at all; neurological symptoms are rarely reversible. Manganese toxicity is generally recognized to...
progress through 3 stages. Levy describes these stages. “The first stage is a prodrome of malaise, somnolence, apathy, emotional lability, sexual dysfunction, weakness, lethargy, anorexia, and headaches. If there is continued exposure, progression to a second stage may occur, with psychological disturbances, including impaired memory and judgment, anxiety, and sometimes psychotic manifestations such as hallucinations. The third stage consists of progressive bradykinesia, dysarthrian axial and extremity dystonia, paresis, gait disturbances, cogwheel rigidity, intention tremor, impaired coordination, and a mask-like face. Many of those affected may be permanently and completely disabled.”(1) Few cases of manganese deficiency or toxicity due to ingestion have been documented. Only 1% to 3% manganese is absorbed via ingestion, while most of the remaining manganese is excreted in the feces. As listed in the United States National Agriculture Library, manganese adequate intake is 1.6 mg/day to 2.3 mg/day for adults. This level of intake is easily achieved, without supplementation, by a diverse diet including fruits and vegetables, which have higher amounts of manganese than other food types. Patients on a long-term parenteral nutrition should receive manganese supplementation and should be monitored to ensure that circulatory levels of manganese are appropriate.

**Useful For:** Monitoring manganese exposure Nutritional monitoring Clinical trials

**Interpretation:** Manganese in urine represents the excretion of excess manganese from the body. Elevated levels may indicate occupational exposure or excessive nutritional intake. Specimens from normal individuals have very low levels of manganese.

**Reference Values:**
<4.0 mcg/specimen
Reference values have not been established for patients that are <18 years of age.


**Manganese, Blood**

**Clinical Information:** Manganese (Mn) is a trace element that is an essential cofactor for several enzymes, including 1 form of superoxide dismutase and the gluconeogenic enzymes: pyruvate carboxylase and isocitrate dehydrogenase. It circulates in the serum as a metalloprotein complex with any of several proteins. The +2 and +3 states are of biological significance, but speciation in the analysis has not been studied sufficiently to determine its value. The required daily intake of 1 to 6 mg is readily supplied by a normal diet with a diverse mixture of fruits and vegetables. Manganese ores and alloys are refined and used in the making of batteries, welding rods, and high-temperature refractory materials. Environmental exposure occurs from inhalation and ingestion of manganese-containing dust and fumes occurring from the refinement processes. It is likely that inhaled Mn is mobilized up the trachea and swallowed; uptake through the gut is inefficient, about 10%. The major compartment for circulating Mn is the erythrocytes, bound to hemoglobin, with whole blood concentrations of Mn (in patients with normal levels) being 10 times that of the serum. Mn passes from the blood to the tissues quickly. Concentrations in the liver are highest, with 1 mg Mn/kg to 1.5 mg Mn/kg (wet weight) in normal individuals. The half-life of Mn in the body is about 40 days, with elimination primarily through the feces. Only small amounts are excreted in the urine. Environmental sources of Mn can lead to toxicity. The primary sites of toxicity are the central nervous system (CNS) and the liver. Acute exposure to Mn fumes gives rise to symptoms common to many metal exposures including fever, dry mouth, and muscle pain. Chronic exposure of several months or more gives rise to CNS symptoms and rigidity, with increased scores on tremor testing and depression scales, as well as generalized parkinsonian features. Confined-space welders have been extensively studied because of their ongoing exposure to metal fumes, but the reported results are difficult to assign to any single metal as the origin of symptoms because of worksite variability, lack of adequate controls, and analytical issues.(1) Nevertheless, reports frequently describe significant increases in Mn levels in the whole blood (or erythrocytes) and in the CNS of these workers, with some evidence that circulating levels decrease following removal of individuals from sources of exposure. The mechanism of Mn-induced neurotoxicity is not clear. While Parkinsonlike symptoms are found, the
damage to nerve cells appears to be to the globus pallidus, while the nigrostriatal pathway (the focus of abnormality in Parkinson disease) is intact (although some claim it is dysfunctional). Increased levels of Mn in the CNS are not necessarily found in manganism, but this could be due to the use of inadequate analytical methodology. Animal studies, while plentiful and useful for pharmacokinetic modeling and possibly for studying mechanisms of hepatotoxicity, are of little value in extrapolation to CNS aberrations in humans because of species-to-species variability in absorption and distribution, and widely divergent psychological means of evaluation.(2) Elevated levels of whole blood Mn have been reported, with and without CNS symptoms, in patients with hepatitis B virus-induced liver cirrhosis, in patients on total parenteral nutrition (TPN) with Mn supplementation, and in infants born to mothers who were on TPN. The studies in cirrhotic patients with extrapyramidal symptoms indicate a possible correlation between whole blood Mn and that measured by T1-weighted magnetic resonance in the globus pallidus and midbrain, with whole blood Mn levels being 2-fold or more, higher than normal. Increases in whole blood Mn over time may be indicative of future CNS effects. The data on TPN patients is based on anecdotes or small studies and is highly variable, as is that obtained in infants.(3) Behçet disease, a form of chronic systemic vasculitis, has been reported to exhibit 4-fold increase in erythrocyte Mn and it is suggested that increased activity of superoxide dismutase may contribute to the pathogenesis of the disease. Mn has been reported as a contaminant in "garage" preparations of the abused drug methcathinone. Continued use of the drug gives rise to CNS toxicity typical of manganism.(4) Reports of suspected toxicity due to gustatory excess, even the drinking of large quantities of Mn-rich tea, may be dismissed as anecdotal and largely due to chance. For monitoring therapy, whether of environmental exposure, TPN, or cirrhosis, whole blood levels have been shown to correlate well with neuropsychological improvement, although whether the laboratory changes precede the CNS or merely track with them is unclear as yet. It is recommended that both CNS functional testing and laboratory evaluation be used to monitor therapy of these patients. Long-term monitoring of Behçet disease has not been reported, and it is not known if the Mn levels respond to therapy.

**Useful For:** Evaluation of central nervous system symptoms similar to Parkinson disease in manganese miners and processors Characterization of liver cirrhosis Therapeutic monitoring in treatment of cirrhosis, parenteral nutrition-related Mn toxicity and environmental exposure to Mn Evaluation of Behçet disease

**Interpretation:** Whole blood levels above the normal range are indicative of manganism. Values between 1 and 2 times the upper limit of normal may be due to differences in hematocrit and normal biological variation, and should be interpreted with caution before concluding that hypermanganesemia is contributing to the disease process. Values greater than twice the upper limit of normal correlate with disease. For longitudinal monitoring, sampling no more frequently than the half-life of the element (40 days) should be used.

**Reference Values:**
4.7-18.3 ng/mL

**Clinical References:**

**Manganese, Red Blood Cell**

**Reference Values:**
- Manganese, Plasma: <2.0 ng/mL
- Manganese, RBC: 11.0 - 23.0 ng/mL

Manganese is highly concentrated in the cellular elements of blood. Hemolysis of the cellular elements that is unobservable to the naked eye can result in elevated plasma manganese concentrations.
**Manganese, Serum**

**Clinical Information:** Manganese (Mn) is a trace essential element with many industrial uses. The twelfth most abundant element in the earth's crust, nearly all mined manganese is consumed in the production of ferromanganese, which is then used to remove oxygen and sulfur impurities from steel. These industrial processes cause elevated environmental exposures to airborne manganese dust and fumes, which in turn have led to well-documented cases of neurotoxicity among exposed workers. Mining and iron and steel production have been implicated as sources of exposure. Inhalation is the primary source of entry for manganese toxicity. Signs of toxicity may appear quickly, and neurological symptoms are rarely reversible. Manganese toxicity is generally recognized to progress through 3 stages. Levy describes these stages. "The first stage is a prodrome of malaise, somnolence, apathy, emotional lability, sexual dysfunction, weakness, lethargy, anorexia, and headaches. If there is continued exposure, progression to a second stage may occur, with psychological disturbances, including impaired memory and judgment, anxiety, and sometimes psychotic manifestations such as hallucinations. The third stage consists of progressive bradykinesia, dysarthrian axial and extremity dystonia, paresis, gait disturbances, cogwheel rigidity, intention tremor, impaired coordination, and a mask-like face. Many of those affected may be permanently and completely disabled."(1) Few cases of manganese deficiency or toxicity due to ingestion have been documented. Only 1% to 3% manganese is absorbed via ingestion, while most of the remaining manganese is excreted in the feces. As listed in the United States National Agriculture Library, manganese adequate intake is 1.6 mg/day to 2.3 mg/day for adults. This level of intake is easily achieved without supplementation by a diverse diet including fruits and vegetables, which have higher amounts of manganese than other food types. Patients on a long-term parenteral nutrition should receive manganese supplementation and should be monitored to ensure that circulatory levels of manganese are appropriate.

**Useful For:** Monitoring manganese exposure Nutritional monitoring Clinical trials

**Interpretation:** Serum manganese results above the reference values suggest recent exposure.

**Reference Values:**

- <2.4 ng/mL
  - Reference values have not been established for patients that are <18 years of age.

**Clinical References:**
3. Finley J, Davis C: Manganese deficiency and toxicity: Are high or low dietary amounts of manganese cause for concern? Biofactors 1999;10:15-24

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**Manganese/Creatinine Ratio, Random, Urine**

**Clinical Information:** Manganese (Mn) is an essential trace element with many industrial uses. Manganese is the 12th most abundant element in the earth's crust and is used predominantly in the production of steel. These industrial processes cause elevated environmental exposures to airborne manganese dust and fumes, which in turn have led to well-documented cases of neurotoxicity among exposed workers. Mining and iron and steel production have been implicated as sources of exposure. Inhalation is the primary source of entry for manganese toxicity. Signs of toxicity may appear quickly or not at all; neurological symptoms are rarely reversible. Manganese toxicity is generally recognized to progress through 3 stages. Levy describes these stages. "The first stage is a prodrome of malaise, somnolence, apathy, emotional lability, sexual dysfunction, weakness, lethargy, anorexia, and headaches. If there is continued exposure, progression to a second stage may occur, with psychological disturbances, including impaired memory and judgment, anxiety, and sometimes psychotic manifestations such as hallucinations. The third stage consists of progressive bradykinesia, dysarthrian axial and extremity dystonia, paresis, gait disturbances, cogwheel rigidity, intention tremor, impaired coordination, and a mask-like face. Many of those affected may be permanently and completely disabled."(1) Few cases of manganese deficiency or toxicity due to ingestion have been documented. Only 1% to 3% manganese is absorbed via ingestion, while most of the remaining manganese is excreted in the feces. As listed in the
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**Useful For:** Monitoring manganese exposure Nutritional monitoring Clinical trials

**Interpretation:** Manganese in urine represents the excretion of excess manganese from the body, and may be used to monitor exposure or excessive nutritional intake.

**Reference Values:**

<4.0 mcg/g creatinine

Reference values have not been established for patients that are <18 years of age.

**Clinical References:**

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**Mango, IgE**

**Clinical Information:**
Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:**
Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.

**FMBL 57587**

**Mannan Binding Lectin (MBL)**

**Reference Values:**

> 100 ng/mL

Investigators most frequently use 100 ng/mL as the threshold for defining an MBL deficiency. MBL values below this value may be associated with increased susceptibility to infection.

**MBL 81051**

**Mannose-Binding Lectin, Serum**

**Clinical Information:** Mannose-binding lectin (MBL) is a member of the collectin family of proteins that are characterized structurally by the presence of collagenous regions and lectin domains in the same subunit. The subunit structure of MBL is comprised of three 32kDa peptide chains organized in a triple helix with 3 C-terminal lectin domains. Circulating (functional) MBL is comprised of oligomers of subunits (dimers through tetramers account for approximately 75% of circulating MBL) that are associated with an MBL-associated serine protease (MASP). There is a single MBL gene (4 exons) on chromosome 10 with 4 known allelic variants: wild type MBL (A), and 3 mutant forms B, C, and D caused by point mutations in 3 different codons. The mutant forms of MBL form oligomers poorly, and have diminished complement activating activity. Multimeric MBL binds to many different oligosaccharide moieties, including those in the cell walls of many different bacteria, yeasts, and some viruses, including HIV 1, HIV 2, and influenza A. Binding of MBL results in complement activation by the classical pathway through activation of complement 4 (C4) by MASP, and surface bound MBL enhances phagocytosis by interacting with collectin receptors on phagocytic cells. Mutations of MBL codons (homozygous or heterozygous haplotypes) are associated with diminished opsonophagocytic activity and diminished serum levels of MBL measured immunochemically (MBL deficiency). MBL-deficient individuals have increased susceptibility to infection particularly if MBL deficiency occurs concomitantly with another heritable immune system abnormality, eg, C4 null alleles or immunoglobulin class or subclass deficiencies.

**Useful For:** Evaluation of children and adults with a clinical history of recurrent infections Results may be useful for genetic counseling and support aggressive management of recurrent infections in patients with reduced levels of mannose-binding lectin

**Interpretation:** Diminished levels of serum mannose-binding lectin (MBL) are consistent with the diagnosis of MBL deficiency. Levels <7.8 ng/mL are associated with homozygous or mixed heterozygous mutant forms of MBL or mutations in the MBL promoter gene.

**Reference Values:**

> or = 7.8 ng/mL

This reference range applies only to adults.

See Cautions for further information regarding the reference range and clinical interpretation.


**FMPRE 57535**

**Maple Red (Acer rubrum) IgE**

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
**MAPTZ**

**MAPT Gene, Sequence Analysis, 7 Exon Screening Panel**

**Clinical Information:** Frontotemporal dementia is a familial adult-onset, presenile dementia that affects the frontal and temporal cerebral cortices. Clinical presentation is variable and includes changes in behavior, difficulties with language, rigidity, palsy, and saccadic (rapid) eye movement. Symptoms generally begin between 40 and 60 years of age, with mean age of onset at approximately 45 years, and typically last between 5 and 10 years, progressing to severe dementia and mutism. The presentation of frontotemporal dementia may be confused with other dementias, including Alzheimer disease. It is important to distinguish between these different dementias because progression and patient management are different for the various dementias. Based on the immunohistochemical staining, there are 2 main subtypes of frontotemporal lobular degeneration (FTLD): tau-positive FTLD and tau-negative FTLD with ubiquitin-positive inclusions (FTLD-U). Mutations in the MAPT gene have been identified in patients with tau-positive FTLD; mutations in the progranulin gene (GRN) have been identified in patients with FTLD-U. Both MAPT and GRN are located on chromosome 17q21. The MAPT gene encodes the microtubule-associated tau protein. A number of mutations have been identified in the MAPT gene that result in aggregation of the tau protein. Although there is variable expression of disease presentation and severity within and between families, the hallmark neurologic lesion constitutes tau-positive protein inclusion bodies. Most clinically significant mutations are found in exons 9 through 13. Several intronic mutations, associated with alternative splicing of the mRNA, contribute to the variability of expression of the disease traits. Mutations in the MAPT gene have also been identified in cases of progressive supranuclear palsy, corticobasal degeneration, and dementia with epilepsy.

**Useful For:** Aiding in the diagnosis of frontotemporal dementia, progressive supranuclear palsy, corticobasal degeneration, and dementia with epilepsy Distinguishing the diagnosis of frontotemporal dementia from other dementias, including Alzheimer dementia Identifying individuals who are at risk of frontotemporal dementia

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. All variants will be reported in reference to transcript NM_001123066 (build GRCh37 (hg19)).

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**MARE**

**Mare's Milk, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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ectopia lentis). Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disease with significant overlap with Marfan syndrome, but may include involvement of other organ systems and is primarily caused by variants in TGFBR1 and TGFBR2. Features of LDS that are not typical of MFS include craniofacial and neurodevelopmental abnormalities, and arterial tortuosity with increased risk for aneurysm and dissection throughout the arterial tree. Variants of the SMAD3 gene have been reported in families with a LDS-like phenotype with arterial aneurysms and tortuosity and early onset osteoarthritis. Variants of the TGFBR3 gene have also been reported in families with an LDS-like phenotype, although these individuals tended to not have arterial tortuosity. TAAD is a genetic condition primarily involving dilatation and dissection of the thoracic aorta, but may also include aneurysm and dissection of other arteries. TAAD has a highly variable age of onset and presentation, and may involve additional features such as congenital heart defects and other features of connective tissue disease or smooth muscle abnormalities depending on the causative gene. The gene most commonly involved in familial TAAD is ACTA2. For other genes also implicated in TAAD, refer to the table below. The COL3A1 gene causes Ehlers Danlos syndrome, vascular type (type IV), an autosomal dominant connective tissue disease with characteristic facial features, thin, translucent skin, easy bruising, and arterial, intestinal, and uterine fragility. Arterial rupture may be preceded by aneurysm or dissection, or may occur spontaneously. The COL5A1 and COL5A2 genes cause Ehlers Danlos syndrome, classic type (type I and type II), an autosomal dominant connective tissue disorder characterized by skin hyperextensibility, widened atrophic scars, joint hypermobility, smooth, velvety skin, and easy bruising. The FLNA gene causes FLNA-related periventricular nodular heterotopia (PVNH), an X-linked neuronal migration disorder where the majority of affected individuals are female. This condition is characterized by seizures, hyperflexible joints, and cardiac findings, which include thoracic aortic aneurysm and dissection. Some individuals show clinical overlap with EDS. Autosomal dominant variants of the FBN2 gene are known to cause congenital contractural arachnodactyly (CCA), which has several overlapping features with Marfan syndrome, including dolichostenomelia, scoliosis, pectus deformity, arachnodactyly, and a risk for thoracic aortic aneurysm. Variants of the CBS gene cause homocystinuria an autosomal recessive disorder of amino acid metabolism with clinical overlap with Marfan syndrome; including lens dislocation and skeletal abnormalities, as well as increased risk for abnormal blood clotting. Variants in the SKI gene cause Shprintzen-Goldberg syndrome (SGS), an autosomal dominant condition with overlap with LDS and MFS. Distinguishing features of SGS include hypertonia and intellectual disability. Aortic root dilatation is less frequent in SGS than in LDS or MFS, but, when present, it can be severe. Homozygous and compound heterozygous loss of function variants in the SLC2A10 gene have been described in arterial tortuosity syndrome, a condition characterized by generalized tortuosity and elongation of all major arteries in addition to other connective tissue disease features. Variants in the NOTCH1 gene cause aortic valve disease, with individuals displaying a range of aortic valve abnormalities and severe valve calcification. Genes included in Marfan Syndrome and Related Disorders Multi-Gene Panel: Gene Protein Inheritance Known Association ACTA2 Actin, alpha-2, smooth muscle, aorta AD TAAD CBS Cystathionine beta-synthase AR Homocystinuria COL3A1 Collagen, type III, alpha-1 AD Ehlers-Danlos syndrome, vascular type (EDS type IV) COL5A1 Collagen, type V alpha-1 AD Ehlers-Danlos Syndrome, Classic Type (EDS type I, EDS type II) COL5A2 Collagen, type V alpha-2 AD Ehlers-Danlos Syndrome, Classic Type (EDS type I, EDS type II) FBN1 Fibrillin 1 AD Marfan syndrome/TAAD/Ectopia Lentis/MASS phenotype/Shprintzen-Goldberg syndrome/Weill-Marchesani syndrome FBN2 Fibrillin 2 AD Congenital Contractual ArachnodactylyFLNA Filamin A X-linked Ehlers-Danlos syndrome and periventricular nodular heterotopia/X-linked cardiac valvular dysplasia/ otopalatodigital spectrum disorders/TAAD TGFAP5 Microfibril-associated protein 5 AD TAAD MYH11 Myosin, heavy chain 11, smooth muscle AD TAAD MYLK Myosin light chain kinase AD TAAD NOTCH1 Notch, drosophila, homolog of, 1 AD Aortic valve disease/Adams-Oliver Syndrome PRKG1 Protein kinase, cGMP-dependent, type 1 AD TAAD SKI V-SKI avian sarcoma viral oncogene homolog AD Shprintzen-Goldberg syndrome SLC2A10 Solute carrier family 2 (facilitated glucose transporter), member 10 AR Arterial Tortuosity syndrome/TAAD (Autosomal Recessive) SMAD3 Mothers against decapentaplegic, drosophila, homolog of, 3 AD Loeye-Dietz syndrome/TAAD SMAD4 Mothers against decapentaplegic, drosophila, homolog of, 4 AD TAAD/JPS/JPS-HHT TGFBR2 Transforming growth factor, beta-2 AD TAAD TGFB3 Transforming growth factor, beta-3 AD Loeye-Dietz syndrome (Rienhoff syndrome)/TAAD TGFBR1 Transforming growth factor-beta receptor, type 1 AD Loeye-Dietz syndrome/TAAD TGFBR2 Transforming growth factor-beta receptor, type II AD Loeye-Dietz syndrome/TAAD Abbreviations: Autosomal dominant (AD), autosomal recessive (AR); thoracic aortic aneurysm and dissection (TAAD); juvenile polyposis syndrome (JPS); juvenile polyposis syndrome-hereditary hemorrhagic telangiectasia (JPS-HHT) Indications for testing include but are not
limited to: Patients who meet clinical diagnostic criteria (Revised Ghent nosology) for Marfan syndrome
-Patients in whom no specific Marfan or related disorder is evident but for whom there is a clear familial component
-Patients whose family history is consistent with TAAD
-Patients with a personal or family history of thoracic aortic aneurysm and/or dissection or a personal or family history of multiple arterial aneurysms

**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of Marfan syndrome, Loeys-Dietz syndrome, thoracic aortic aneurysm and dissections, or a related disorder Second-tier testing for patients in whom previous targeted gene variant analyses for specific Marfan and related genes were negative Establishing a diagnosis of a Marfan or a related disorder in some cases, allowing for appropriate management and surveillance for aneurysms and other disease features based on the gene involved Identifying variants within genes known to be associated with increased risk for aneurysms and other disease features allowing for predictive testing of at-risk family members

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to interpret in the assistance of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Marjoram, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Reference values apply to all ages.


Mass Spectrometry (Bill Only)

Reference Values:

This test is for billing purposes only.

This is not an orderable test.

MatePair, Targeted Rearrangements, Congenital

Clinical Information: De novo apparently balanced chromosome rearrangements are found in approximately 1 in 1,000 individuals. Although they appear balanced at the level of resolution from a G-banded chromosome analysis, 6% of these individuals have an abnormal phenotype that is twice the
background risk. This has led to speculation that submicroscopic gene disruption or dysregulation may explain the abnormal phenotype in these individuals. Mate-pair sequencing is a next-generation sequencing technology that can aid in the further characterization of chromosome abnormalities by sequencing the entire genome and bioinformatically mapping short fragments of the genome to create a structural map of the genome. This technique enables the mapping of chromosome rearrangements to a resolution of approximately 2 kilobases or less, which allows for determination of genes at or near the breakpoints.

**Useful For:** Second-tier testing when previous cytogenetic testing has detected a constitutional/congenital chromosome abnormality of unknown significance Determining the size, precise breakpoints, gene content, and any unappreciated complexity of abnormalities identified by conventional chromosome studies Providing important diagnostic, prognostic, and therapeutic information critical to proper patient management

**Interpretation:** The interpretation describes the further characterization of the previously identified chromosome abnormality. When possible the interpretation will state how this finding might be associated with the patient's abnormal phenotype. The continual discovery of novel genes, gene functions, and published clinical reports means that the interpretation of any finding may evolve with increased scientific understanding.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**MTRBM 64935**

**MatePair, Targeted Rearrangements, Hematologic**

**Clinical Information:** While many hematologic neoplasms (leukemias and lymphomas) have a subset of common or well-characterized acquired chromosome abnormalities, sometimes patients are found to have acquired chromosome abnormalities of uncertain significance. Further characterization of these abnormalities may lead to a better understanding of their pathogenicity and potentially lead to prognostic information or guide treatment and management of the patient. Mate-pair sequencing is a next-generation sequencing technology that can aid in the further characterization of chromosome abnormalities by sequencing the entire genome and bioinformatically mapping short fragments of the genome to create a structural map of the genome. This technique enables the mapping of chromosome rearrangements to a resolution of approximately 2 kilobases or less, which allows for determination of genes at or near the breakpoints.

**Useful For:** Second-tier testing in hematologic specimens when previous cytogenetic or FISH testing have detected an acquired chromosome abnormality of unknown significance Determining the size, precise breakpoints, gene content, and any unappreciated complexity of abnormalities detected by other methods such as conventional chromosome and FISH studies Providing important diagnostic, prognostic, and therapeutic information critical to proper patient management

**Interpretation:** The interpretation describes the further characterization of the previously identified acquired abnormality. When possible, the interpretation will state how this finding might be associated with the hematologic process and any potential information on diagnosis, prognosis, and treatment options given the finding. The continual discovery of novel structural rearrangements and published clinical reports means that the interpretation of any finding may evolve with increased scientific understanding. Although the presence of a clonal abnormality usually indicates a neoplasia, in some situations it may reflect a benign or constitutional genetic change. If a genetic change is identified that is likely constitutional and clearly pathogenic, follow-up with a medical genetics consultation may be suggested. The absence of an abnormal clone may be the result of specimen collection from a site that is not involved in the neoplasm or may indicate that the genetic abnormality is not detectable by this assay.

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
**Reference Values:**
An interpretive report will be provided.


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**MatePair, Targeted Rearrangements, Oncology**

**Clinical Information:** While many tumors have a subset of common or well-characterized acquired chromosome abnormalities, some tumors may be found to have acquired chromosome abnormalities of uncertain significance. Further characterization of these abnormalities may lead to a better understanding of their pathogenicity and potentially lead to prognostic information or guide treatment/management of the patient. Mate-pair sequencing is a next-generation sequencing technology that can aid in the further characterization of chromosome abnormalities by sequencing the entire genome and bioinformatically mapping short fragments of the genome to create a structural map of the genome. This technique enables the mapping of chromosome rearrangements to a resolution of approximately 2 kilobases or less, which allows for determination of genes at/near the breakpoints.

**Useful For:** Second-tier testing in oncologic specimens when previous cytogenetic testing has detected an acquired chromosome abnormality of unknown significance Determining the size, precise breakpoints, gene content, and any unappreciated complexity of abnormalities detected by other methods such as conventional chromosome and FISH studies Providing important diagnostic, prognostic, and therapeutic information critical to proper patient management

**Interpretation:** The interpretation describes the further characterization of the previously identified acquired abnormality. When possible, the interpretation will state how this finding might be associated with the neoplastic process and any potential information on diagnosis, prognosis, and/or treatment options given the finding. The continual discovery of novel structural rearrangements and published clinical reports means that the interpretation of any finding may evolve with increased scientific understanding. Although the presence of a clonal abnormality usually indicates a neoplasia, in some situations it may reflect a benign or constitutional genetic change. If a genetic change is identified that is likely constitutional and clearly pathogenic, follow-up with a medical genetics consultation may be suggested. The absence of an abnormal clone may be the result of specimen collection from a site that is not involved in the neoplasm, or may indicate that the genetic abnormality is not detectable by this assay.

**Reference Values:**
An interpretive report will be provided.


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**Maternal Cell Contamination, Molecular Analysis**

**Clinical Information:** One of the risks associated with prenatal testing is maternal cell contamination (MCC), which can occur when a fetal specimen comes into contact with maternal blood or tissue. The risk of MCC is associated with procedures such as chorionic villus sampling, amniocentesis, or extraction of fetal blood from the umbilical cord (cord blood). If MCC is present, the maternal DNA may mask the results of any genetic testing performed on the fetal DNA. Therefore, the results of prenatal testing may be compromised. To rule out the presence of MCC, a maternal blood specimen is necessary for comparison of maternal and fetal chromosomal markers. The presence of both
maternal and nonmaternal alleles for each fetal marker indicates the fetal specimen is not contaminated. MCC is confirmed when both alleles in the fetus are maternal.

**Useful For:** Ruling out the presence of maternal cell contamination within a fetal specimen This test is required for all prenatal testing performed in Mayo's molecular and biochemical genetics laboratories

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretative report will be provided.

Clinical Information: This test combines a first-and-second-trimester specimen to screen low-risk pregnancies for Down syndrome (DS), open neural tube defects (ONTD) and trisomy 18 (T18). Collection of two blood samples is required for this test. A first trimester ultrasound to measure the fetal nuchal translucency (NT) is optional (see special instructions). Patient demographics and analyte/ultrasound measurements are used to calculate multiple of the median (MoM) values for each of the laboratory analytes and the NT. The pattern of the MoM values is used to calculate post-test risks for ONTD, DS and T18. Markers used for assessment of risk include first-trimester PAPP-A with or without NT and second-trimester AFP, hCG, unconjugated estriol (uE3), and dimeric Inhibin A. A DS risk of 1 in 110 or worse is reported as abnormal. This risk cutoff predicts a detection rate of 87 percent at a screen positive rate of 1.0%. A T18 risk of 1 in 100 or worse is reported as abnormal. This risk cutoff predicts a detection rate of 90 percent at a screen positive rate of <0.5%. ARUP uses a singleton AFP MoM cutoff of >or=2.5. If the interpretation is "high AFP," there is an increased risk of an ONTD in the pregnancy. This cutoff value predicts a detection rate of 80% at a screen positive rate of 1.5%. High AFP also occurs in unrecognized twin pregnancies and with underestimated gestational age. Pregnancies at an increased risk for ONTD with an AFP MoM <2.5, but a risk of 1 in 250 or worse, are also reported as abnormal. This is usually due to a family history of ONTD, the use of certain seizure medications by the patient during pregnancy, or the presence of maternal insulin-dependent diabetes, any of which increases a patient's priori risk for ONTD. An increased risk of congenital steroid sulfatase deficiency or Smith-Lemli-Opitz syndrome (uE3 <or=0.14 MoM) and poor fetal outcome (hCG >or=3.5 MoM) is reported as "see note."

Useful For: Helpful to identify pregnancies at increased risk of having a child with Down syndrome (trisomy 21), Open Neural Tube Defect (ONTD, spina bifida) and trisomy 18 (T18). This test is not diagnostic. The patient information provided with the Integrated, Specm1 will be used to calculate the risks for this report.

Interpretation: An interpretive report will be provided. See clinical information sections. Part 2 must be completed in order to receive an interpretable result. If the second specimen is not received for sequential screening, the results are uninterpretable and no maternal risk will be provided.

Reference Values:
An interpretive report will be provided.

Mayo Algorithmic Approach for Stratification of Myeloma and Risk-Adapted Therapy Report

Clinical Information: Multiple myeloma is increasingly recognized as a disease characterized by marked cytogenetic, molecular, and proliferative heterogeneity. This heterogeneity is manifested clinically by varying degrees of disease aggressiveness. Multiple myeloma patients with more aggressive disease experience suboptimal responses to some therapeutic approaches; therefore, identifying these patients is critically important for selecting appropriate treatment options. Mayo Algorithmic Approach for Stratification of Myeloma and Risk-Adapted Therapy (MSMRT) classifies patients into either standard or high-risk categories based on the results of 2 assays: plasma cell proliferation and FISH for specific multiple myeloma-associated abnormalities.

Useful For: Risk stratification of patients with multiple myeloma, which can assist in determining treatment and management decisions Risk stratification of patients with newly diagnosed multiple myeloma

Interpretation: An interpretive report is provided. Patients are classified as high risk, intermediate, or standard risk.

Reference Values:
Plasma Cell Clonality:
- Normal bone marrow
- No monotypic clonal plasma cells detected
DNA Index:
- Normal polytypic plasma cells
DNA index (G0/G1 cells): Diploid 0.95-1.05


MDM2F

**MDM2 (12q15) Amplification, Well-Differentiated Liposarcoma/Atypical Lipomatous Tumor, FISH, Tissue**

Clinical Information: The histological discrimination of well-differentiated liposarcoma/atyypical lipomatous tumor (WDL/ALT) from lipoma can be diagnostically challenging. However, standard cytogenetic identification of ring and giant rod chromosomes strongly support the diagnosis of WDL/ALT. These abnormal chromosomes are mainly composed of amplified sequences derived from chromosome bands 12q13-15, and contain several amplified genes including MDM2, CPM, CDK4, and TSPAN31. MDM2 is amplified in >99% of WDL, and up to 30% of other types of sarcomas.

Useful For: Supporting a diagnosis of well-differentiated liposarcoma/atyypical lipomatous tumor

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for the MDM2 FISH probe (positive result). A positive result is consistent with amplification of the MDM2 gene locus (12q15) and supports the diagnosis of well-differentiated liposarcoma/atyypical lipomatous tumor (WDL/ALT). A negative result is consistent with absence of amplification of the MDM2 gene locus (12q15). However, negative results do not exclude the diagnosis of WDL/ALT. Amplification varies in individual tumors and among different cells in the same tumor.

Reference Values:
An interpretive report will be provided.


MEAD

**Meadow Fescue, IgE**

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>0</td>
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<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


MFOX 82914

Meadow Foxtail, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<th>Interpretation</th>
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</table>

**Measles (Rubeola) Antibodies, IgG, Serum**

**Clinical Information:** The measles virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1-4, mumps, respiratory syncytial virus (RSV), and metapneumovirus. The measles virus is one of the most highly contagious infectious diseases among unvaccinated individuals and is transmitted through direct contact with aerosolized droplets or other respiratory secretions from infected individuals. Measles has an incubation period of approximately 8 to 12 days, which is followed by a prodromal phase of high fever, cough, coryza, conjunctivitis, and malaise. Koplik spots may also be apparent on the buccal mucosa and can last for 12 to 72 hours. Following this phase, a maculopapular, erythematous rash develops beginning behind the ears and on the forehead and spreading centrifugally to involve the trunk and extremities. Immunocompromised individuals, pregnant women, and those with nutritional deficiencies are particularly at risk for serious complications following measles infection, which include pneumonia and central nervous system involvement.

Following implementation of the national measles vaccination program in 1963, the incidence of measles infection has fallen to fewer than 0.5 cases per 1,000,000 population and the virus is no longer considered endemic in the United States. Measles outbreaks continue to occur in the United States due to exposure of nonimmune individuals or those with waning immunity to infected travelers. The measles outbreak in 2011 throughout Western Europe emphasizes the persistence of the virus in the worldwide population and the continued need for national vaccination programs.

The diagnosis of measles infection is often based on clinical presentation alone. Screening for IgG-class antibodies to measles virus will aid in identifying nonimmune individuals.

**Useful For:** Determination of immune status of individuals to the measles virus

**Interpretation:** Positive: Antibody index (AI) value of 1.1 or higher

The reported AI value is for reference only. This is a qualitative test and the numeric value of the AI is not indicative of the amount of antibody present. AI values above the manufacturer recommended cutoff for this assay indicate that specific antibodies were detected, suggesting prior exposure or vaccination. The presence of detectable IgG-class antibodies indicates prior exposure to the measles virus through infection or immunization. Individuals testing positive are considered immune to measles infection. Equivocal: AI value 0.9-1.0

Submit an additional sample for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative: AI value of 0.8 or lower

The absence of detectable IgG-class antibodies suggests the lack of a specific immune response to immunization or no prior exposure to the measles virus.

**Reference Values:**

- **Vaccinated:** positive (> or =1.1 AI)
- **Unvaccinated:** negative (< or =0.8 AI)
Reference values apply to all ages.

**Clinical References:**

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**Measles (Rubeola) Antibodies, IgM, Serum**

**Clinical Information:** The measles virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1-4, mumps, respiratory syncytial virus (RSV), and metapneumovirus. The measles virus is among the most highly contagious infectious diseases among unvaccinated individuals and is transmitted through direct contact with aerosolized droplets or other respiratory secretions from infected individuals. Measles has an incubation period of approximately 8 to 12 days, which is followed by a prodromal phase of high fever, cough, coryza, conjunctivitis, and malaise. Koplik spots may also be apparent on the buccal mucosa and can last for 12 to 72 hours.(1,2) Following this phase, a maculopapular, erythematous rash develops beginning behind the ears and on the forehead and spreading centrifugally to involve the trunk and extremities. Immunocompromised individuals, pregnant women, and those with nutritional deficiencies, are particularly at risk for serious complications following measles infection, which include pneumonia and central nervous system involvement.(1,3) Following implementation of the national measles vaccination program in 1963, the incidence of measles infection has fallen to below 0.5 cases per 1,000,000 population and the virus is no longer considered endemic in the United States.(4) Measles outbreaks continue to occur in the United States due to exposure of nonimmune individuals or those with waning immunity to infected travelers. The measles outbreak in 2011 throughout Western Europe emphasizes the persistence of the virus in the worldwide population and the continued need for national vaccination programs.(5) The diagnosis of measles infection is often based on clinical presentation alone. The presence of IgM-class antibodies suggests recent infection, but should not be used alone to diagnose measles infection. Screening for IgG-class antibodies to measles virus aids in identifying nonimmune individuals.

**Useful For:** Determining acute-phase infection with rubeola (measles) virus using IgM antibody testing Aiding in the identification of nonimmune individuals through IgM antibody testing

**Interpretation:** This assay tests only for IgM-class antibody. For both IgM and IgG antibody testing, see ROGM / Measles (Rubeola) Virus Antibody, IgM and IgG (Separate Determinations), Serum. The presence of IgM-class antibodies, with or without the presence of IgG-class antibodies to measles virus may support a clinical diagnosis of recent/acute phase infection with the virus. IgM results alone should not be used to diagnose measles virus infection. The absence of IgM-class antibodies suggests lack of an acute phase infection with measles virus. However serology may be negative for IgM-class antibodies in early disease, and results should be interpreted in the context of clinical findings. Testing for IgM-class antibodies to measles should be limited to patients with clinically compatible disease. The presence of detectable IgG-class antibodies, in the absence of IgM-class antibodies, indicates prior exposure to the measles virus through infection or immunization. These individuals are considered immune to measles infection. The absence of detectable IgG-class antibodies suggests the lack of a specific immune response to immunization or no prior exposure to the measles virus. These individuals are considered nonimmune to measles virus infection.

**Reference Values:**
Negative
Reference values apply to all ages.

**Clinical References:**
Measles (Rubeola) Virus Antibody, IgM and IgG (Separate Determinations), Serum

**Clinical Information:** The measles virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1-4, mumps, respiratory syncytial virus (RSV), and metapneumovirus. The measles virus is among the most highly contagious infectious diseases among unvaccinated individuals and is transmitted through direct contact with aerosolized droplets or other respiratory secretions from infected individuals. Measles has an incubation period of approximately 8 to 12 days, which is followed by a prodromal phase of high fever, cough, coryza, conjunctivitis, and malaise. Koplik spots may also be apparent on the buccal mucosa and can last for 12 to 72 hours.(1,2) Following this phase, a maculopapular, erythematous rash develops beginning behind the ears and on the forehead and spreading centrifugally to involve the trunk and extremities. Immunocompromised individuals, pregnant women, and those with nutritional deficiencies, are particularly at risk for serious complications following measles infection, which include pneumonia and central nervous system involvement.(1,3) Following implementation of the national measles vaccination program in 1963, the incidence of measles infection has fallen to below 0.5 cases per 1,000,000 population and the virus is no longer considered endemic in the United States.(4) Measles outbreaks continue to occur in the United States due to exposure of nonimmune individuals or those with waning immunity to infected travelers. The measles outbreak in 2011 throughout Western Europe emphasizes the persistence of the virus in the worldwide population and the continued need for national vaccination programs.(5) The diagnosis of measles infection is often based on clinical presentation alone. The presence of IgM-class antibodies suggests recent infection, but should not be used alone to diagnose measles infection. Screening for IgG-class antibodies to measles virus aids in identifying nonimmune individuals.

**Useful For:** Laboratory diagnosis of measles virus infection Determination of immune status of individuals to the measles virus using IgG antibody testing Documentation of previous infection with measles virus in an individual without a previous record of immunization to measles virus

**Interpretation:** This assay tests for both IgM and IgG-class antibodies. The presence of IgM-class antibodies, with or without the presence of IgG-class antibodies to measles virus may support a clinical diagnosis of recent/acute phase infection with the virus. IgM results alone should not be used to diagnose measles virus infection. The absence of IgM-class antibodies suggests lack of an acute phase infection with measles virus. However serology may be negative for IgM-class antibodies in early disease, and results should be interpreted in the context of clinical findings. Testing for IgM-class antibodies to measles should be limited to patients with clinically compatible disease. The presence of detectable IgG-class antibodies, in the absence of IgM-class antibodies, indicates prior exposure to the measles virus through infection or immunization. These individuals are considered immune to measles infection. The absence of detectable IgG-class antibodies suggests the lack of a specific immune response to immunization or no prior exposure to the measles virus. These individuals are considered nonimmune to measles virus infection.

**Reference Values:**

**IgM**

Negative
Reference values apply to all ages.

**IgG**

Vaccinated: positive (≥ 1.1 A.I)
Unvaccinated: negative (< 0.8 A.I)
Reference values apply to all ages.

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**Meconium Methadone Screen**

**Reference Values:**
The specimen was screened by Immunoassay at the following threshold concentrations:
Methadone: 50 ng/gm

Positive results are confirmed by Chromatography with Mass Spectrometry (GC/MS) to limit of detection.

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**MECP2 Gene, Full Gene Analysis**

**Clinical Information:** Methyl-CpG-binding protein 2 (MeCP2) is a transcriptional repressor protein encoded by the MECP2 gene located on the X chromosome. Genetic mutations in MECP2 alter the expression of targeted genes and can be associated with variable phenotypes in females including classic Rett syndrome, variant or atypical Rett syndrome, mild mental retardation, and asymptomatic carriers. Males with MECP2 mutations can present with variable phenotypes as well. The variability in males can, in part, be attributed to the type of MECP2 mutation present; point mutations are typically associated with severe neonatal encephalopathy and gene duplications are associated with MECP2 duplication syndrome. Full MECP2 gene analysis via sequencing and large duplication/deletion studies has been useful in identifying germline mutations in individuals with these clinical presentations.

**Rett Syndrome:** Rett syndrome is an X-linked, panethnic condition with an incidence of approximately 1 in 8,500 to 1 in 15,000 females. Disease course typically begins after 6 to 18 months of apparently normal development with rapid regression in language and motor skills. A hallmark feature of this condition is repetitive, stereotyped hand movements, sometimes described as hand-wringing. Clinical criteria have been established for diagnosis of classic and atypical or variant Rett syndrome. Greater than 88% of females with a clinical diagnosis of classic Rett syndrome demonstrate a mutation by this test. The detection rate is approximately 43% for females with a clinical diagnosis of atypical or variant Rett syndrome. For individuals in whom there is clinical suspicion for Rett syndrome, but clinical criteria are not met, the detection rate is lower given the phenotypic overlap with other conditions (eg, Angelman syndrome). Nonrandom X chromosome inactivation, resulting in phenotypic variability within families, has been reported in females with MECP2 mutations. Although 99.5% of mutations associated with Rett syndrome are de novo, asymptomatic or very mildly affected carrier mothers of classically affected daughters have been reported. Genetic counseling should be provided with this, and the possibility of germline or somatic mosaicism, in mind. MECP2 Duplication Syndrome: Although MECP2 mutations are reported in males, these males typically do not present with classic Rett syndrome unless an abnormal karyotype (ie, 47,XXY) or somatic mosaicism is also present. More commonly, MECP2 mutations have been reported in karyotypically normal males presenting with neonatal encephalopathy and mental retardation syndromes. MECP2 duplication syndrome is an increasingly reported severe mental retardation syndrome characterized by infantile hypotonia, absence of speech, and progressive spasticity. Seizures and recurrent respiratory infections are commonly reported as well. These MECP2 gene duplications vary in size from 0.3 to 2.3 Mb. Although chromosome analysis can identify some larger duplications, other methods such as multiplex ligation-dependent probe amplification (MLPA) can identify essentially all MECP2 gene duplications. Males with nongene-duplication type mutations can present with other mental retardation syndromes (ie, Angelman-like syndrome) or neonatal encephalopathy and early death. To date, all males found to have an MECP2 duplication are clinically affected and have inherited the duplication from their asymptomatic mothers. Therefore, mothers of...
sons with MECP2 duplication syndrome are thought to be obligate carriers whose male offspring have a 50% risk of being affected.

**Useful For:** Diagnosis of Rett syndrome or other MECP2-related disorders

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**MCADZ**

**Medium-Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency Full Gene Analysis**

**Clinical Information:** Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is an autosomal recessive inherited defect in the mitochondrial oxidation of fatty acids. The mitochondrial beta-oxidation pathway plays a major role in energy production, especially during periods of fasting and physical exertion. MCAD deficiency is prevalent among individuals of northern European origin, affecting 1 in 4,900 to 1 in 17,000 individuals, with a carrier frequency estimated as high as 1 in 40 for some populations. Phenotypic expression of MCAD deficiency is episodic in nature (ie, asymptomatic between attacks). Symptoms are typically precipitated by any stress (eg, fever, infection, vaccination) and mostly occur during the first 2 years of life, although some cases have been diagnosed in adulthood. Characteristic features of MCAD deficiency include: Reye-like syndrome (an acquired encephalopathy characterized by recurrent vomiting, agitation, and lethargy), fasting intolerance with vomiting, recurrent episodes of hypoglycemic coma, hypoketotic dicarboxylic aciduria, low plasma and tissue levels of carnitine, hepatic failure with fat infiltration (fatty liver), encephalopathy, and rapidly progressive deterioration leading to death. MCAD deficiency has also been associated with sudden infant death or sudden unexpected death syndrome. Review of clinical features and biochemical analysis via plasma acylcarnitines (ACRN / Acylcarnitines, Quantitative, Plasma), fatty acid profile (FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture), urine organic acids (OAU / Organic Acids Screen, Urine), and urine acylglycines (ACYLG / Acylglycines, Quantitative, Urine) are always recommended as the initial evaluation for MCAD. If previously performed, the results of these biochemical assays should be included with the specimen as they are necessary for accurate interpretation of the MCAD sequence analysis. The MCAD gene (ACADM) maps to 1p31 and has 12 exons, spanning 44 kb of DNA. Most mutations are family-specific with the exception of the recurrent A->G transition at nucleotide 985 (985A->G). Among MCAD-deficient patients, approximately 52% are homozygous for the 985A->G mutation. The majority of the remaining patients are compound heterozygous for the 985A->G mutation and a different mutation.

**Useful For:** Confirmation of diagnosis of medium-chain acyl-CoA dehydrogenase (MCAD) deficiency (as a follow-up to biochemical analyses) Screening of at-risk carriers of MCAD deficiency when an affected relative has not had molecular testing Diagnosis of MCAD deficiency in autopsy specimens.
**MEDF**

**58122**

**Medulloblastoma, FISH, Tissue**

**Clinical Information:** Medulloblastoma is the most common malignant brain tumor in children. Current treatment decisions are based on clinical variables. Biomarkers have been identified that allow classification of medulloblastoma into subtypes that are associated with a specific clinical behavior. FISH analyses for the MYCN, MYB, and MYC loci may be useful in medulloblastoma patients to help provide prognostic information and guide treatment.

**Useful For:** Identifying MYCN amplification, MYC amplification, and monosomy of chromosome 6 (detected using MYB probe), to aid in the classification of medulloblastoma patients into specific clinical categories

**Interpretation:** MYCN: -The MYCN locus is reported as amplified when the MYCN:D2Z1 ratio is 2.0 or greater and demonstrates 8 or more copies of the MYCN locus. -A tumor with a MYCN:D2Z1 ratio <2.0 or demonstrating a ratio of 2.0 or greater with <8 copies of MYCN, is considered to lack amplification of the MYCN locus. MYB: Monosomy of chromosome 6 is reported when the percent of cells with the abnormality exceeds the normal cutoff for the probe set. MYC: -The MYC locus is reported as amplified when the MYC:D8Z2 ratio is 2.0 or greater and demonstrates 8 or more copies of the MYC locus. -A tumor with a MYC:D8Z2 ratio <2.0 or demonstrating a ratio of 2.0 or greater with <8 copies of MYC, is considered to lack amplification of the MYC locus.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**MEFVZ**

**35486**

**MEFV Gene, Full Gene Analysis**

**Clinical Information:** Familial Mediterranean fever (FMF) is a hereditary auto-inflammatory disease which is most prevalent in Mediterranean populations (Turks, Armenians, Sephardic Jews, Arabs), where the incidence is approximately 1 in 400 to 1 in 1000. FMF has been reported in other
populations as well. FMF is characterized by recurrent febrile episodes with associated abdominal pain, pleuritis, arthritis, and, rarely, pericarditis and meningitis. Attacks typically occur 1 to 2 times per month and last 1 to 3 days. Age of onset is typically before 10 years. Amyloid A (AA) type amyloidosis is a severe complication of FMF which can lead to renal failure. Clinical features vary and some individuals with FMF present with amyloidosis as the first clinical manifestation of disease (classified as FMF type 2). FMF is caused by mutations in the MEFV gene encoding pyrin. FMF is typically inherited in an autosomal recessive fashion, but heterozygous mutation carriers may also develop symptoms. Ongoing prophylactic treatment with colchicine has been shown to reduce frequency and severity of febrile attacks and inhibit development of amyloidosis in the majority of patients with FMF. In particular, patients with 1 or 2 copies of the M694V mutation are typically responsive to colchicine treatment.

**Useful For:** Confirmation of familial Mediterranean fever (FMF) for patients with clinical features

**Interpretation:** All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics (AMCG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**MEGR 82347**

**Megrim, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
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</table>
Melaleuca leucadendron, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
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</table>

Reference values apply to all ages.

**MELAN 70504**

**Melan A (MART-1) Immunostain, Technical Component Only**

**Clinical Information:** Melanoma antigen recognized by T cells or Melan-A (MART-1), is a protein with unknown function that is associated with endoplasmic reticulum and melanosomes. Melan A is a sensitive and specific marker for the diagnosis of melanoma. Melan A is also found in other tumors of melanocytic origin such as clear cell sarcoma, melanotic neurofibroma, melanotic schwannoma, as well as in perivascular epithelioid cell tumor. The monoclonal antibody A103 for Melan A cross-reacts with steroid hormone producing cells and tumors. Consequently, adrenocortical adenomas/carcinomas and sex cord-stromal tumors of the ovary and testis may exhibit staining.

**Useful For:** Aids in the identification of melanoma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**MELP 35343**

**Melanoma Targeted Gene Panel by Next-Generation Sequencing, Tumor**

**Clinical Information:** Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the FDA for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Next generation sequencing has recently emerged as an accurate, cost-effective method to identify mutations across numerous genes known to be associated with response or resistance to specific targeted therapies. MELP / Melanoma Targeted Gene Panel by Next Generation Sequencing, Tumor is a single assay that uses formalin-fixed paraffin-embedded tissue to assess for common mutations in the following genes known to be associated with melanoma: BRAF, GNA11, GNAQ, KIT, and NRAS. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with melanoma. See Targeted Gene Regions Interrogated by Melanoma Panel in Special Instructions for details regarding the targeted gene regions identified by this test.

**Useful For:** Diagnosis and management of patients with melanoma
**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Melanoma, FISH, Tissue**

**Clinical Information:** Melanocytic tumors arising in the skin can present a significant diagnostic challenge. While many lesions can be easily classified as benign nevi or malignant melanoma based on histologic features alone, there is a significant subset of lesions that cannot be clearly defined as either benign or malignant. Because the course of treatment for malignant melanoma relative to benign lesions varies significantly from the time of diagnosis, accuracy, and expediency of the diagnosis are of paramount importance. A FISH-based test panel has been developed that can be used as a diagnostic aid in the differentiation of malignant from benign melanocytic lesions. This test is intended to be used in conjunction with clinical and pathologic information to aid the pathologist in the differentiation of benign from malignant melanocytic lesions.

**Useful For:** An aid in the differentiation of benign from malignant melanocytic lesions when used in conjunction with clinical and pathologic information

**Interpretation:** The panel test is considered abnormal if certain parameters are met that have been shown to be observed in malignant melanocytic lesions and within normal limits if these parameters are not met. An abnormal result is not diagnostic of malignancy, nor does a normal result exclude malignancy. The results are intended to be interpreted in the context of the pathologic and clinical findings.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FMELP**

**Melatonin, Plasma**

**Interpretation:** Endogenous concentrations of melatonin are of the order of less than 0.02-0.2 ng/mL and vary based on time of day and age. An oral use of a 6 mg dose in 60 female subjects produced an average peak concentration of 12 ng/mL with a peak time of approximately 0.75 hours. A 10 mg dose in male subjects produced an average concentration of 9.8 ng/mL. Melatonin's major side effect profile includes drowsiness and sleepiness.

**Reference Values:**

Reporting limit: 1.0 ng/mL

**FMELG**

**Melons IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**MELN**

**Melons, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


FMEP 90090
Meperidine (Demerol) and Normeperidine, serum
Clinical Information: Category: Narcotic Analgesic
Reference Values:
Meperidine:
Reference Range: 400 - 700 ng/ml
Normeperidine: No reference range provided

FMMM 57766
Mephedrone, MDPV and Methylnone, Urine
Reference Values:
Drug Units Reference Range
---------------------------------------------------------------
Mephedrone Negative
MDPV Negative
Methylnone Negative

Qualitative analysis for Mephedrone, Methylenedioxyxpyrovalerone (MDPV) and Methylnone
Screening threshold: 1.0 ng/mL

MEPHS 83778
Mephobarbital and Phenobarbital, Serum
Clinical Information: Mephobarbital is an orally administered, methylated barbiturate used for the treatment of epilepsy.(1,2) It is demethylated by hepatic microsomal enzymes to generate its major metabolite, phenobarbital. During long-term use, most of mephobarbital's activity can be attributed to the accumulation of phenobarbital. Consequently, mephobarbital's pharmacological properties, toxicity, and clinical uses are the same as phenobarbital's.(1,2) The use of mephobarbital is uncommon as it offers no significant advantage over phenobarbital alone.(1,2)

Useful For: Monitoring of mephobarbital and phenobarbital therapy

Interpretation: Mephobarbital concentrations above 15 mcg/mL have been associated with toxicity. Phenobarbital concentrations between 35 and 80 mcg/mL have been associated with slowness, ataxia, and nystagmus, while concentrations above 100 have been associated with coma without reflexes.
**Reference Values:**

**MEPHOBARBITAL**
Therapeutic range: 1.0-7.0 mcg/mL
Toxic concentration: > or =15.0 mcg/mL

**PHENOBARBITAL**
Therapeutic range
Children: 15.0-30.0 mcg/mL
Adults: 20.0-40.0 mcg/mL
Toxic concentration: > or =60.0 mcg/mL


**FMERC**

**Mercaptopurine (6-MP, Purinethol)**

**Reference Values:**
Units: ng/mL

Mercaptopurine may be administered as an antineoplastic or may be present as a metabolite of the immunosuppressant drug azathioprine. Therapeutic and toxic ranges have not been established. Usual therapeutic doses of either mercaptopurine or azathioprine produce 6-mercaptopurine serum concentrations of less than 1000 ng/mL.

**HGUO**

**Mercury Occupational Exposure, Random, Urine**

**Clinical Information:** The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor. However, urinary Hg is the most reliable way to assess exposure to inorganic Hg. For additional information, see HG / Mercury, Blood.

**Useful For:** Detecting mercury toxicity due to occupational exposure

**Interpretation:** Daily urine excretion of mercury greater than 50 mcg/day indicates significant exposure (per World Health Organization standard).

**Reference Values:**
Biological Exposure Index (BEI): <35 mcg/g creatinine prior to shift


**HGU**

**Mercury, 24 Hour, Urine**

**Clinical Information:** The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor. However, urinary Hg is the most reliable way to assess exposure to inorganic Hg. For additional information, see HG / Mercury, Blood.

**Useful For:** Detecting mercury toxicity in 24-hour urine specimens

**Interpretation:** Daily urine excretion of mercury above 50 mcg/day indicates significant exposure (per World Health Organization standard).
Reference Values:
0-17 years: not established
> or =18 years: <2 mcg/24 hour
Toxic concentration: >50 mcg/24 hour
The concentration at which toxicity is expressed is widely variable between patients. 50 mcg/24 hour is the lowest concentration at which toxicity is usually apparent.


Mercury, Blood

Clinical Information: Mercury (Hg) is essentially nontoxic in its elemental form. If Hg(0) is chemically modified to the ionized, inorganic species, Hg(+2), it becomes toxic. Further bioconversion to an alkyl Hg, such as methyl Hg (CH[3]Hg(+)), yields a species of mercury that is highly selective for lipid-rich tissue such as neurons and is very toxic. The relative order of toxicity is: Not Toxic - Hg(0) < Hg(+2) << CH(3)Hg(+) -- Very Toxic Mercury can be chemically converted from the elemental state to the ionized state. In industry, this is frequently done by exposing Hg(0) to strong oxidizing agents such as chlorine. Hg(0) can be bioconverted to both Hg(+2) and alkyl Hg by microorganisms that exist both in the normal human gut and in the bottom sediment of lakes, rivers, and oceans. When Hg(0) enters bottom sediment, it is absorbed by bacteria, fungi, and small microorganisms; they metabolically convert it to Hg(+2), CH(3)Hg(+), and (CH[3])(+2)Hg. Should these microorganisms be consumed by larger marine animals and fish, the mercury passes up the food chain in rather toxic form. Mercury expresses its toxicity in 3 ways: -Hg(+2) is readily absorbed and reacts with sulfhydryl groups of protein, causing a change in the tertiary structure of the protein-a stereoisomeric change-with subsequent loss of the unique activity associated with that protein. Because Hg(+2) becomes concentrated in the kidney during the regular clearance processes, this target organ experiences the greatest toxicity. -With the tertiary change noted previously, some proteins become immunogenic, eliciting a proliferation of T lymphocytes that generate immunoglobulins to bind the new antigen; collagen tissues are particularly sensitive to this. -Alkyl Hg species, such as CH(3)Hg(+), are lipophilic and avidly bind to lipid-rich tissues such as neurons. Myelin is particularly susceptible to disruption by this mechanism. Members of the public will occasionally become concerned about exposure to mercury from dental amalgams. Restorative dentistry has used a mercury-silver amalgam for approximately 90 years as a filling material. A small amount of mercury (2-20 mcg/day) is released from a dental amalgam when it was mechanically manipulated, such as by chewing. The habit of gum chewing can cause release of mercury from dental amalgams greatly above normal. The normal bacterial flora present in the mouth converts a fraction of this to Hg(+2) and CH(3)Hg(+), which was shown to be incorporated into body tissues. The World Health Organization safety standard for daily exposure to mercury is 45 mcg/day. Thus, if one had no other source of exposure, the amount of mercury released from dental amalgams is not significant.(1) Many foods contain mercury. For example, commercial fish considered safe for consumption contain <0.3 mcg/g of mercury, but some game fish contain >2.0 mcg/g and, if consumed on a regular basis, contribute to significant body burdens. Therapy is usually monitored by following urine output; therapy may be terminated after urine excretion is <50 mcg/day.

Useful For: Detecting mercury toxicity

Interpretation: The quantity of mercury (Hg) found in blood and urine correlates with degree of toxicity. Hair analysis can be used to document the time of peak exposure if the event was in the past. Normal whole blood mercury is usually <10 ng/mL. Individuals who have mild exposure during work, such as dentists, may routinely have whole blood mercury levels up to 15 ng/mL. Significant exposure is indicated when the whole blood mercury is >50 ng/mL if exposure is due to alkyl Hg, or >200 ng/mL if exposure is due to Hg(+2).

Reference Values:
Normal: 0-9 ng/mL
Reference values apply to all ages.

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**Mercury, Hair**

**Clinical Information:** Once absorbed and circulating, mercury becomes bound to numerous proteins, including keratin. The concentration of mercury in hair correlates with the severity of clinical symptoms. If the hair can be segregated by length, such an exercise can be useful in identifying the time of exposure.

**Useful For:** Detecting mercury exposure in hair specimens

**Interpretation:** Normally, hair contains less than 1 mcg/g of mercury; any amount more than this indicates that exposure to more than normal amounts of mercury has occurred.

**Reference Values:**

- 0-15 years: not established
- > or =16 years: 0.0-0.9 mcg/g of hair


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**Mercury, Nails**

**Clinical Information:** Once absorbed and circulating, mercury becomes bound to numerous proteins, including keratin. The concentration of mercury in nails correlates with the severity of clinical symptoms. If the nails can be segregated by length, such an exercise can be useful in identifying the time of exposure.

**Useful For:** Detecting mercury exposure

**Interpretation:** Normally, nails contain less than 1 mcg/g of mercury; any amount more than this indicates that exposure to more than normal amounts of mercury has occurred.

**Reference Values:**

- 0-15 years: not established
- > or =16 years: 0.0-0.9 mcg/g of nails


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**Mercury/Creatinine Ratio, Random, Urine**

**Clinical Information:** The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor. However, urinary Hg is the most reliable way to assess exposure to inorganic Hg. For additional information, see HG / Mercury, Blood.
Mercury/Creatinine Ratio, Random, Urine

Clinical Information: The correlation between the levels of mercury (Hg) excretion in the urine and the clinical symptoms is considered poor. However, urinary Hg is the most reliable way to assess exposure to inorganic Hg. For additional information, see HG / Mercury, Blood.

Useful For: Detecting mercury toxicity in random urine specimens

Interpretation: Daily urine excretion of mercury above 50 mcg/day indicates significant exposure (per World Health Organization standard).

Reference Values:
Only orderable as part of profile. See HGCR / Mercury/Creatinine Ratio, Random, Urine or HMCUR / Heavy Metal/Creatinine Ratio, with Reflex, Urine.


Merkel CC (MCPyV) Immunostain, Technical Component Only

Clinical Information: Merkel cell polyomavirus (MCPyV) infections are common and typically benign. In rare instances, these infections lead to neoplastic transformations known as Merkel cell carcinoma (MCC) through the expression (nuclear) of MCPyV large T-antigen. MCPyV-positive MCC have been reported to behave less aggressively than MCPyV-negative MCC.

Useful For: Identification of Merkel cell polyomavirus (MCPyV) infected cells

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**HEY1**

**Mesenchymal Chondrosarcoma, by Reverse Transcriptase PCR (RT-PCR)**

**Clinical Information:** Mesenchymal chondrosarcoma is a rare sarcoma of bone and soft tissues. The histological diagnosis of mesenchymal chondrosarcoma can be challenging especially in small biopsy samples. HEY1-NCOA2 fusion transcript has been identified in more than 90% of mesenchymal chondrosarcoma, but not in other soft tissue tumors.

**Useful For:** Supporting a diagnosis of mesenchymal chondrosarcoma when pathological examination is insufficient for diagnosis.

**Interpretation:** A HEY1-NCOA2 fusion transcript positive result supports a diagnosis of mesenchymal chondrosarcoma but a negative result does not necessarily rule-out a diagnosis of mesenchymal chondrosarcoma.

**Reference Values:**
An interpretative report will be provided.


**MESOR**

**Mesoridazine (Serentil)**

**Reference Values:**
Reference Range: 150 - 1000 ng/mL

**HBME**

**Mesothelial Cell (HBME-1) Immunostain, Technical Component Only**

**Clinical Information:** This mesothelial cell (HBME-1) antibody stains an unknown antigen in the microvillus processes of mesothelial cells with a “thick membrane” staining pattern. The antibody also reacts with a wide variety of normal and neoplastic tissues. This stain is diagnostically useful in distinguishing thyroid carcinoma (papillary and follicular types) from thyroid follicular adenomas, which usually lack staining.

**Useful For:** Aids in the classification of thyroid carcinomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic.
Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Reference Values:**
N/A

**Clinical References:**
3. Rosai J: Immunohistochemical Markers of Thyroid Tumors: Significance and Diagnostic Applications. Tumori 2003;89(5):517-519

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**Mesquite, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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**Clinical References:** Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and
MET (7q31), FISH, Tissue

Clinical Information: MET is a proto-oncogene and its overexpression is associated with disease progression. Recent studies have shown MET amplification to be a major mechanism of acquired resistance to epidermal growth factor receptor tyrosine kinase domain inhibitor (EGFR-TKI). MET amplification has been reported in approximately 5% of patients not treated with EGFR-TKI and up to 20% of patients with acquired resistance to gefitinib or erlotinib.

Useful For: Providing prognostic information and guiding treatment primarily for patients with lung, gastric, and renal tumors as well as other tumor types

Interpretation: A positive result is detected when the MET:D7Z1 ratio is $\geq 2.0$. The MET locus is reported as amplified when the MET:D7Z1 ratio of 2.0 or greater. Patients with 5 or more copies of MET have a poor prognosis. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References:

Metabolic Myopathy Panel (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

Metabolic/Syndromic Neuropathy Panel by Next-Generation Sequencing (NGS)

Clinical Information: Inherited peripheral neuropathies are a relatively common diverse group of disorders with heterogeneous genetic causes. Due to the considerable overlap in the clinical phenotypes of various neuropathies, it is often difficult to distinguish these specific inherited disorders from sporadic, idiopathic, or acquired forms of neuropathy without genetic testing. Additionally, peripheral neuropathy may be part of an inherited systemic syndromic or metabolic disorder caused by genes in metabolic pathways. Given the considerable phenotypic overlap and the broad genetic heterogeneity of inherited peripheral neuropathies, a comprehensive diagnostic genetic test is useful to establish the genetic cause in this group of inherited diseases. See Targeted Genes Interrogated by Metabolic/Syndromic Neuropathy Panel in Special Instructions for details regarding the targeted genes identified by this test.

Useful For: Diagnosis of an inherited metabolic or syndromic neuropathy associated with known causal genes Second-tier testing for patients in whom previous targeted gene mutation analyses for specific inherited metabolic or syndromic neuropathy genes where negative Identifying mutations within genes known to be associated with inherited metabolic or syndromic neuropathy, allowing for predictive
testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**METAF 83006**

**Metanephrines, Fractionated, 24 Hour, Urine**

**Clinical Information:** Pheochromocytoma is a rare, though potentially lethal, tumor of chromaffin cells of the adrenal medulla that produces episodes of hypertension with palpitations, severe headaches, and sweating (“spells”). Patients with pheochromocytoma may also be asymptomatic and present with sustained hypertension or an incidentally discovered adrenal mass. Pheochromocytomas and other tumors derived from neural crest cells (eg, paragangliomas and neuroblastomas) secrete catecholamines (epinephrine, norepinephrine, and dopamine). Metanephrine and normetanephrine are the 3-methoxy metabolites of epinephrine and norepinephrine, respectively. Metanephrine and normetanephrine are both further metabolized to vanillylmandelic acid. Pheochromocytoma cells also have the ability to oxymethylate catecholamines into metanephrines that are secreted into circulation. In patients that are highly suspect for pheochromocytoma it may be best to screen by measuring plasma free fractionated metanephrines (a more sensitive assay). The 24-hour urinary fractionated metanephrines (a more specific assay) may be used as the first test for low suspicion cases and also as a confirmatory study in patients with a less than 2-fold elevation in plasma free fractionated metanephrines. This is highly desirable, as the very low population incidence rate of pheochromocytoma (<1:100,000 population per year) will otherwise result in large numbers of unnecessary, costly, and sometimes risky imaging procedures. Complete 24-hour urine collections are preferred, especially for patients with episodic hypertension; ideally the collection should begin at the onset of a "spell."

**Useful For:** A first- and second-order screening test for the presumptive diagnosis of catecholamine-secreting pheochromocytomas and paragangliomas Confirming positive plasma metanephrine results

**Interpretation:** Increased metanephrine and normetanephrine levels are found in patients with pheochromocytoma and tumors derived from neural crest cells. Total urine metanephrines 1,300 mcg/24 hours and lower can be detected in nonpheochromocytoma hypertensive patients. Further clinical investigation (eg, radiographic studies) is warranted in patients whose total urinary metanephrine levels are above 1,300 mcg/24 hours (approximately 2 times the upper limit of normal). For patients with total urinary metanephrine levels below 1,300 mcg/24 hours, further investigations may also be indicated if either the normetanephrine or the metanephrine fraction of the total metanephrines exceed their respective upper limit for hypertensive patients. Finally, repeat testing or further investigations may occasionally be indicated in patients with urinary metanephrine levels below the hypertensive cutoff, or even normal levels, if there is a very high clinical index of suspicion.

**Reference Values:**

<table>
<thead>
<tr>
<th>METANEPHRINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Normotensives</td>
</tr>
</tbody>
</table>
9-12 years: 59-188 mcg/24 hours
13-17 years: 69-221 mcg/24 hours
> or =18 years: 44-261 mcg/24 hours
Reference values have not been established for patients that are <36 months of age.

Females
Normotensives
3-8 years: 18-144 mcg/24 hours
9-12 years: 43-122 mcg/24 hours
13-17 years: 33-185 mcg/24 hours
> or =18 years: 30-180 mcg/24 hours
Reference values have not been established for patients that are <36 months of age.

Hypertensives: <400 mcg/24 hours

NORMETANEPHRINE
Males
Normotensives
3-8 years: 34-169 mcg/24 hours
9-12 years: 84-422 mcg/24 hours
13-17 years: 91-456 mcg/24 hours
18-29 years: 103-390 mcg/24 hours
30-39 years: 111-419 mcg/24 hours
40-49 years: 119-451 mcg/24 hours
50-59 years: 128-484 mcg/24 hours
60-69 years: 138-521 mcg/24 hours
> or =70 years: 148-560 mcg/24 hours
Reference values have not been established for patients that are <36 months of age.

Hypertensives: <900 mcg/24 hours

Females
Normotensives
3-8 years: 29-145 mcg/24 hours
9-12 years: 55-277 mcg/24 hours
13-17 years: 57-286 mcg/24 hours
18-29 years: 103-390 mcg/24 hours
30-39 years: 111-419 mcg/24 hours
40-49 years: 119-451 mcg/24 hours
50-59 years: 128-484 mcg/24 hours
60-69 years: 138-521 mcg/24 hours
> or =70 years: 148-560 mcg/24 hours
Reference values have not been established for patients that are <36 months of age.

Hypertensives: <900 mcg/24 hours

TOTAL METANEPHRINE
Males
Normotensives
3-8 years: 47-223 mcg/24 hours
9-12 years: 201-528 mcg/24 hours
13-17 years: 120-603 mcg/24 hours
18-29 years: 190-583 mcg/24 hours
30-39 years: 200-614 mcg/24 hours
40-49 years: 211-646 mcg/24 hours
50-59 years: 222-680 mcg/24 hours
60-69 years: 233-716 mcg/24 hours
> or =70 years: 246-753 mcg/24 hours
Reference values have not been established for patients that are <36 months of age.

Hypertensives: <1,300 mcg/24 hours

Females
Normotensives
3-8 years: 57-210 mcg/24 hours
9-12 years: 107-394 mcg/24 hours
13-17 years: 113-414 mcg/24 hours
18-29 years: 142-510 mcg/24 hours
30-39 years: 149-535 mcg/24 hours
40-49 years: 156-561 mcg/24 hours
50-59 years: 164-588 mcg/24 hours
60-69 years: 171-616 mcg/24 hours
> or =70 years: 180-646 mcg/24 hours

Reference values have not been established for patients that are <36 months of age.
Hypertensives: <1,300 mcg/24 hours

For SI unit Reference Values, see


PMET 81609

Metanephrines, Fractionated, Free, Plasma

Clinical Information: Pheochromocytoma is a rare, though potentially lethal, tumor of chromaffin cells of the adrenal medulla that produces episodes of hypertension with palpitations, severe headaches, and sweating ("spells"). Patients with pheochromocytoma may also be asymptomatic and present with sustained hypertension or an incidentally discovered adrenal mass. Pheochromocytomas and other tumors derived from neural crest cells (eg, paragangliomas and neuroblastomas) secrete catecholamines (epinephrine, norepinephrine, and dopamine). Metanephrine and normetanephrine (collectively referred to as metanephrines) are the 3-methoxy metabolites of epinephrine and norepinephrine, respectively. The metanephrines are stable metabolites and are cosecreted directly with catecholamines by pheochromocytomas and other neural crest tumors. This results in sustained elevations in plasma free metanephrine levels, making them more sensitive and specific than plasma catecholamines in the identification of pheochromocytoma patients. (1) Metanephrine and normetanephrine are both further metabolized to conjugated metanephrines and vanillylmandelic acid.

Useful For: Screening test for presumptive diagnosis of catecholamine-secreting pheochromocytomas or paragangliomas

Interpretation: In the normal population, plasma metanephrine and normetanephrine levels are low, but in patients with pheochromocytoma or paragangliomas, the concentrations may be significantly elevated. This is due to the relatively long half-life of these compounds, ongoing secretion by the tumors and, to a lesser degree, peripheral conversion of tumor-secreted catecholamines into metanephrines. Measurement of plasma free metanephrines appears to be the best test for excluding pheochromocytoma. The test's sensitivity approaches 100%, making it extremely unlikely that individuals with normal plasma metanephrine and normetanephrine levels suffer from pheochromocytoma or paraganglioma. (1,2) Due to the low prevalence of pheochromocytomas and related tumors (<1:100,000), it is recommended to confirm elevated plasma free metanephrines with a second, different testing strategy in order to avoid large numbers of false-positive test results. (3) The recommended second-line test is measurement of fractionated 24-hour urinary metanephrines (METAFT / Metanephrines, Fractionated, 24 Hour, Urine). In most cases this strategy will suffice in confirming or excluding the diagnosis. Occasionally, it will be necessary to extend this approach if there is a very high clinical index of suspicion or if test results are nonconclusive. In these cases, repeat plasma and urinary metanephrines testing, additional measurement of plasma or urinary catecholamines, or imaging procedures might be indicated. Elevated results are reported with appropriate comments.

Reference Values:
METANEPHRINE, FREE
<0.50 nmol/L

NORMETANEPHRINE, FREE
<0.90 nmol/L


Metanephrines, Fractionated, Random, Urine

Clinical Information: Pheochromocytoma is a rare, though potentially lethal, tumor of chromaffin cells of the adrenal medulla that produces episodes of hypertension with palpitations, severe headaches, and sweating ("spells"). Pheochromocytomas and other tumors derived from neural crest cells (e.g., paragangliomas and neuroblastomas) secrete catecholamines (epinephrine and norepinephrine). Metanephrine and normetanephrine are the 3-methoxy metabolites of epinephrine and norepinephrine, respectively. Metanephrine and normetanephrine are both further metabolized to vanillylmandelic acid. Pheochromocytoma cells also have the ability to oxymethylate catecholamines into metanephrines that are secreted into circulation. While screening for pheochromocytoma is best accomplished by measuring plasma free fractionated metanephrines (a more sensitive assay), follow-up testing with urinary fractionated metanephrines (a more specific assay) may identify false-positives. Twenty-four hour urine collections are preferred, especially for patients with episodic hypertension; ideally the collection should begin at the onset of a "spell."

Useful For: A second-order screening test for the presumptive diagnosis of pheochromocytoma in patients with nonepisodic hypertension Confirming positive plasma metanephrine results in patients with nonepisodic hypertension

Interpretation: Increased metanephrine and normetanephrine levels are found in patients with pheochromocytoma and tumors derived from neural crest cells. Increased urine metanephrines can be detected in nonpheochromocytoma hypertensive patients; quantification may help distinguish these patients from those with tumor-induced symptoms.

Reference Values:

METANEPHRINE/CREATININE
Normotensives
0-2 years: 82-418 mcg/g creatinine
3-8 years: 65-332 mcg/g creatinine
9-12 years: 41-209 mcg/g creatinine
13-17 years: 30-154 mcg/g creatinine
> or =18 years: 29-158 mcg/g creatinine

NORMETANEPHRINE/CREATININE
Males
Normotensives
0-2 years: 121-946 mcg/g creatinine
3-8 years: 92-718 mcg/g creatinine
9-12 years: 53-413 mcg/g creatinine
13-17 years: 37-286 mcg/g creatinine
18-29 years: 53-190 mcg/g creatinine
**30-39 years:** 60-216 mcg/g creatinine  
**40-49 years:** 69-247 mcg/g creatinine  
**50-59 years:** 78-282 mcg/g creatinine  
**60-69 years:** 89-322 mcg/g creatinine  
**> or =70 years:** 102-367 mcg/g creatinine

**Females**  
**Normotensives**  
**0-2 years:** 121-946 mcg/g creatinine  
**3-8 years:** 92-718 mcg/g creatinine  
**9-12 years:** 53-413 mcg/g creatinine  
**13-17 years:** 37-286 mcg/g creatinine  
**18-29 years:** 81-330 mcg/g creatinine  
**30-39 years:** 107-436 mcg/g creatinine  
**40-49 years:** 122-500 mcg/g creatinine  
**50-59 years:** 141-574 mcg/g creatinine  
**> or =70 years:** 161-659 mcg/g creatinine

### TOTAL METANEPHRINE/CREATININE

**Males**  
**Normotensives**  
**0-2 years:** 241-1,272 mcg/g creatinine  
**3-8 years:** 186-980 mcg/g creatinine  
**9-12 years:** 110-582 mcg/g creatinine  
**13-17 years:** 78-412 mcg/g creatinine  
**18-29 years:** 96-286 mcg/g creatinine  
**30-39 years:** 106-316 mcg/g creatinine  
**40-49 years:** 117-349 mcg/g creatinine  
**50-59 years:** 130-386 mcg/g creatinine  
**60-69 years:** 143-427 mcg/g creatinine  
**> or =70 years:** 159-472 mcg/g creatinine

**Females**  
**Normotensives**  
**0-2 years:** 241-1,272 mcg/g creatinine  
**3-8 years:** 186-980 mcg/g creatinine  
**9-12 years:** 110-582 mcg/g creatinine  
**13-17 years:** 78-412 mcg/g creatinine  
**18-29 years:** 131-467 mcg/g creatinine  
**30-39 years:** 147-523 mcg/g creatinine  
**40-49 years:** 164-585 mcg/g creatinine  
**50-59 years:** 184-655 mcg/g creatinine  
**60-69 years:** 206-733 mcg/g creatinine  
**> or =70 years:** 230-821 mcg/g creatinine

**Clinical References:**  

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**FMETF**

**Metformin, Serum/Plasma**

**Reference Values:**

Reporting limit determined each analysis
Therapeutic range: Approximately 1–2 mcg/mL. Metformin associated lactic acidosis generally has been associated with Metformin plasma concentrations exceeding 5 mcg/mL.

**Methadone and Metabolites, Serum**

**Clinical Information:** Methadone, a long-acting synthetic opioid analgesic, is an agonist at the mu receptor. It has several actions qualitatively similar to those of morphine, primarily involving the central nervous system and organs composed of smooth muscles. Analgesia, sedation, and detoxification or maintenance in opioid addiction can be achieved with therapeutic use of methadone hydrochloride. Methadone acts by binding to the mu-opioid receptor, but also has some affinity for the N-methyl-D-aspartate receptor (NMDA) ionotropic glutamate receptor. Methadone undergoes extensive biotransformation in the liver. Methadone is metabolized by CYP3A4, CYP2B6, CYP2C19, and CYP2D6 enzymes. It is also a substrate for the P-glycoprotein efflux protein. The major inactive metabolite is a result of N-demethylation and cyclization, and forms 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP). Substantial interindividual and intraindividual variability in metabolism and elimination has been noted. The half-life of methadone is highly variable and typically ranges from 7 to 59 hours; however, longer half-lives have been reported.

**Useful For:** Compliance monitoring of methadone. Assessment of toxicity.

**Interpretation:** There is a significant overlap between the reported therapeutic and toxic concentrations of methadone in blood specimens.

**Reference Values:**
Not established

**Clinical References:**

**Methadone Confirmation, Chain of Custody, Urine**

**Clinical Information:** Methadone (dolophine) is a synthetic opioid, a compound that is structurally unrelated to the natural opiates but is capable of binding to opioid receptors. These receptor interactions create many of the same effects seen with natural opiates, including analgesia and sedation. However, methadone does not produce feelings of euphoria and has substantially fewer withdrawal symptoms than opiates such as heroin. Methadone is used clinically to relieve pain, to treat opioid abstinence syndrome, and to treat heroin addiction in the attempt to wean patients from illicit drug use. Metabolism of methadone to inactive forms is the main form of elimination. Oral delivery of methadone makes it subject to first-pass metabolism by the liver and creates interindividual variability in its bioavailability, which ranges from 80% to 95%. The most important enzymes in methadone metabolism are CYP3A4 and CYP2B6. CYP2D6 appears to have a minor role, and CYP1A2 may possibly be involved. Methadone is metabolized to a variety of metabolites, the primary metabolite is 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP). The efficiency of this process is prone to wide inter- and intraindividual variability, due both to inherent differences in enzymatic activity as well as enzyme induction or inhibition by numerous drugs. Excretion of methadone and its metabolites (including EDDP) occurs primarily through the kidneys. Patients who are taking methadone for therapeutic purposes excrete both parent methadone and EDDP in their urine. Clinically, it is important to measure levels of both methadone and EDDP. Methadone levels in urine vary widely depending on
factors such as dose, metabolism, and urine pH. EDDP levels, in contrast, are relatively unaffected by the influence of pH and are, therefore, preferable for assessing compliance with therapy. Some patients undergoing treatment with methadone have attempted to pass compliance testing by adding a portion of the supplied methadone to the urine. This is commonly referred to as "spiking." In these situations the specimen will contain large amounts of methadone and no or very small amounts of EDDP. The absence of EDDP in the presence of methadone in urine strongly suggests adulteration of the urine specimen by direct addition of methadone to the specimen. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Monitoring of methadone treatment for analgesia or drug rehabilitation. Urine measurement of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine is particularly useful for assessing compliance with rehabilitation programs. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** The absolute concentration of methadone and its metabolites found in patient urine specimen can be highly variable and do not correlate with dose. However, the medical literature and our experience show that patients who are known to be compliant with their methadone therapy have ratios of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP):methadone of >0.60. An EDDP: methadone ratio <0.090 strongly suggests manipulation of the urine specimen by direct addition of methadone to the specimen.

**Reference Values:**

- **Negative**

  - **Cutoff concentrations:**
    - IMMUNOASSAY SCREEN
      - <300 ng/mL
    - METHADONE BY GC-MS
      - <100 ng/mL
    - 2-ETHYLIDENE-1,5-DIMETHYL-3,3-DIPHENYLPYRROLIDINE BY GC-MS
      - <100 ng/mL

**Clinical References:**

4. Baselt RC: Disposition of Toxic Drugs and Chemicals in Man. Seventh edition. Foster City, CA, Chemical Toxicology Institute, 2005

**Clinical Information:** Methadone (Dolophine) is a synthetic opioid, a compound that is structurally unrelated to the natural opiates but is capable of binding to opioid receptors. These receptor interactions create many of the same effects seen with natural opiates, including analgesia and sedation. However, methadone does not produce feelings of euphoria and has substantially fewer withdrawal symptoms.
than opiates such as heroin. Methadone is used clinically to relieve pain, to treat opioid abstinence syndrome, and to treat heroin addiction in the attempt to wean patients from illicit drug use. Metabolism of methadone to inactive forms is the main form of elimination. Oral delivery of methadone makes it subject to first-pass metabolism by the liver and creates interindividual variability in its bioavailability, which ranges from 80% to 95%. The most important enzymes in methadone metabolism are CYP3A4 and CYP2B6. CYP2D6 appears to have a minor role, and CYP1A2 may possibly be involved. Methadone is metabolized to a variety of metabolites, the primary metabolite is 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP). The efficiency of this process is prone to wide inter- and intraindividual variability, due both to inherent differences in enzymatic activity as well as enzyme inhibition or induction by numerous drugs. Excretion of methadone and its metabolites (including EDDP) occurs primarily through the kidneys. Patients who are taking methadone for therapeutic purposes excrete both parent methadone and EDDP in their urine. Clinically, it is important to measure levels of both methadone and EDDP. Methadone levels in urine vary widely depending on factors such as dose, metabolism, and urine pH. EDDP levels, in contrast, are relatively unaffected by the influence of pH and are, therefore, preferable for assessing compliance with therapy. Some patients undergoing treatment with methadone have attempted to pass compliance testing by adding a portion of the supplied methadone to the urine. This is commonly referred to as "spiking." In these situations the specimen will contain large amounts of methadone and no or very small amounts of EDDP. The absence of EDDP in the presence of methadone in urine strongly suggests adulteration of the urine specimen by direct addition of methadone to the specimen.

**Useful For:** Monitoring of methadone treatment for analgesia or drug rehabilitation. Urine measurement of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine is particularly useful for assessing compliance with rehabilitation programs.

**Interpretation:** The absolute concentration of methadone and its metabolites found in patient urine specimen can be highly variable and do not correlate with dose. However, the medical literature and our experience show that patients who are known to be compliant with their methadone therapy have ratios of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP):methadone of >0.60. An EDDP:methadone ratio <0.090 strongly suggests manipulation of the urine specimen by direct addition of methadone to the specimen.

**Reference Values:**

- **Negative**
- Cutoff concentrations:

  - METHADONE BY GC-MS
    - <100 ng/mL
  - 2-ETHYLIDENE-1,5-DIMETHYL-3,3-DIPHENYLPYRROLIDINE BY GC-MS
    - <100 ng/mL

**Clinical References:**

4. Baselt RC: Disposition of Toxic Drugs and Chemicals in Man. Seventh edition. Foster City, CA, Chemical Toxicology Institute, 2005
**Interpretation:** Methaqualone, ng/mL. Report Limit 50 ng/mL. Reference Range 500-80000 ng/mL. Critical Value High 160000 ng/mL.

**Reference Values:**

ng/mL

Results are reported to the limit of quantitation for the analysis.

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**Methemoglobin and Sulfhemoglobin, Blood**

**Clinical Information:** Methemoglobin: When iron in hemoglobin is oxidized from the normal divalent state to a trivalent state, the resulting brownish pigment is methemoglobin. Methemoglobin cannot combine reversibly with oxygen and is associated with cyanosis. Methemoglobinemia, with or without sulfhemoglobinemia, is most commonly encountered as a result of administration of medications such as phenacetin, phenazopyridine, sulfonamides, local anesthetics, dapsone, or following ingestion of nitrates or nitrites. Congenital methemoglobinemias are rare. They are either due to: - Deficiency of methemoglobin reductase (also called cytochrome B5 reductase or diaphorase) in erythrocytes, an autosomal recessive disorder. - One of several intrinsic structural disorders of hemoglobin, called methemoglobin-M, all of which are inherited in the autosomal dominant mode. Methemoglobinemia responds to treatment with methylene blue or ascorbic acid. Sulfhemoglobin: Sulfhemoglobin cannot combine with oxygen. Sulfhemoglobinemia is associated with cyanosis and often accompanies drug-induced methemoglobinemia. Sulfhemoglobinemia can be due to exposure to trinitrotoluene or zinc ethylene bisdithiocarbamate (a fungicide), or by ingestion of therapeutic doses of flutamide. In contrast to methemoglobinemia, sulfhemoglobinemia persists until the erythrocytes containing it are destroyed. Therefore, blood level of sulfhemoglobin declines gradually over a period of weeks. Patients with sulfhemoglobinemia often also have methemoglobinemia. There is no specific treatment for sulfhemoglobinemia. Therapy is directed at reversing the methemoglobinemia, if present.

**Useful For:** Diagnosing methemoglobinemia and sulfhemoglobinemia. Identifying cyanosis due to other causes, such as congenital heart disease.

**Interpretation:** In congenital methemoglobinemia, the methemoglobin concentration in blood is about 15% to 20% of total hemoglobin. Such patients are mildly cyanotic and asymptomatic. In acquired (toxic) methemoglobinemia, the concentration may be much higher. Symptoms may be severe when methemoglobin is >40% of hemoglobin. Very high concentrations (>70%) may be fatal.

**Reference Values:**

**METHEMOGLOBIN**

- 0-11 months: not established
- > or =1 year: 0.0-1.5% of total hemoglobin

**SULFHEMOGLOBIN**

- 0-11 months: not established
- > or =1 year: 0.0-0.4% of total hemoglobin


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**Methemoglobin Reductase, Blood**

**Clinical Information:** Methemoglobin reductase, also called "diaphorase," and more properly called cytochrome b5 reductase, is the enzyme within the erythrocyte that maintains hemoglobin in the reduced (non-methemoglobin) state. Persons who are heterozygous for methemoglobin reductase mutations have no clinical or laboratory abnormalities, are not cyanotic, and have normal methemoglobin concentrations in their blood. However, they hold an increased risk for more severely symptomatic acute episodes of methemoglobinemia with exposure to inducing agents. Persons who are
homozygous for methemoglobin reductase mutations have normal arterial oxygen saturation but have varying quantities of methemoglobin in their blood, generally 15% to 20%, and are quite cyanotic. Paradoxically, homozygotes typically have normal blood counts; the condition only rarely causes polycythemia. The presence of methemoglobin shifts the hemoglobin-O2 dissociation curve to the right, so that although the transport of oxygen is diminished, the delivery of oxygen to tissues is normal. Because of the chronicity, the homozygous condition is usually compensated and therefore quite benign, but may cause concern to parents of affected children, be a cosmetic embarrassment to the children, and alarm the attending physician. The cyanosis may be treated with methylene blue.

**Useful For:**

- Confirming cases of suspected methemoglobin reductase (cytochrome b5 reductase) deficiency
- Functional studies in families with methemoglobin reductase (cytochrome b5 reductase) deficiency

**Interpretation:**

Methemoglobin reductase (cytochrome b5 reductase) activity in neonates (0-6 weeks) is normally 60% of the normal adult value. Adult values are attained by 2 to 3 months of age. Heterozygotes have results slightly lower than the reference range. Homozygotes demonstrate little to no methemoglobin reductase activity and increased levels of methemoglobin.

**Reference Values:**

- 
  > or =12 months: 6.6-13.3 U/g Hb
  - Reference values have not been established for patients who are <12 months of age.

**Clinical References:**


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**Methemoglobinemia Evaluation**

**Clinical Information:**

Methemoglobin: Methemoglobin forms when the hemoglobin molecule iron is in the ferric (Fe3+) form instead of the functional ferrous (Fe2+) form. Methemoglobinemia can be hereditary or acquired and is present by definition when methemoglobin levels are greater than the normal range. Acquired methemoglobinemia results after toxic exposure to nitrates and nitrites/nitrates (fertilizer, nitric oxide), topical anesthetics ("caines"), dapsone, naphthalene (moth balls/toilet deodorant cakes) and industrial use of aromatic compounds (aniline dyes). Congenital methemoglobinemias are rare. They are due either to:

- A deficiency of methemoglobin reductase (also called NADH-cytochrome b5 reductase 3 or diaphorase) in erythrocytes, an autosomal recessive disorder resulting from mutations in the CYB5R3 or the CYB5A genes. Type IV is thought to be extraordinarily rare. Type III is no longer a category.
- One of several intrinsic structural disorders of hemoglobin, called M-hemoglobins (M-Hbs), all of which are inherited in an autosomal dominant manner. Classically, M-Hbs result from histidine-to tyrosine substitutions at the proximal or distal histidine important in coordinating the oxygen molecule. These include alpha-, beta- and gamma-chain variants. Rarely, other substitutions outside the proximal and distal histidine location can cause Hb variants that increase methemoglobin or sulfhemoglobin levels. Most M-hemoglobin variants are readily identified by HPLC or mass spectrometry methods with characteristic electrophoresis patterns; however, some require more specialized techniques. Most are associated with increased methemoglobin with or without an increase in sulfhemoglobin. Alpha chain M-hemoglobin variants can be associated with increased sulfhemoglobin without an increase in methemoglobin.

Sulfhemoglobin: Sulfhemoglobinemia often accompanies methemoglobinemia. Sulfhemoglobinemia can be due to exposure to trinitrotoluene, zinc ethylene bisdithiocarbamate (a fungicide), overexposure to paint or varnish fumes, metoclopramide, sulfonamides and some migraine medications. The formation of sulfhemoglobin cannot be reversed and there is no therapy for sulfhemoglobinemia aside from removal of the inciting agent. Because patients with sulfhemoglobinemia also often have methemoglobinemia, therapy is directed at reversing the methemoglobinemia present. Isolated increased sulfhemoglobin levels can also be associated with alpha chain M-hemoglobin variants. Symptoms of both methemoglobinemia and sulfhemoglobinemia are characterized by cyanosis.

**Useful For:**

- Diagnosis of methemoglobinemia and sulfhemoglobinemia and possible hereditary (congenital) causes
- Differentiation of methemoglobinemia and sulfhemoglobinemia from other causes of cyanosis (eg, congenital heart disease)
**Interpretation:** In congenital methemoglobinemia, the methemoglobin concentration in blood is about 15% to 20% of total hemoglobin. Such patients are mildly cyanotic and asymptomatic. In acquired (toxic) methemoglobinemia, the concentration may be much higher. Symptoms may be severe when methemoglobin is greater than 40% of hemoglobin. Very high concentrations may be fatal. This is a consultative evaluation in which the history and previous laboratory values are reviewed by a hematologist who is an expert on these disorders. Appropriate tests are performed and an interpretive report is issued.

**Reference Values:**
Definitive results and an interpretive report will be provided.

**Clinical References:**

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**MTXSG 62580 Methotrexate Post Glucarpidase, Serum**

**Clinical Information:** Methotrexate, an antimetabolite (folate reductase inhibitor), is used at high dose (12 gm/m^2[2]) to treat neoplastic diseases, such as lymphocytic leukemia. Therapy is guided by measurement of serum concentration: 24 hours after dosage, the serum concentration should be <10 mcmol/L; 48 hours after therapy, concentration should be <1 mcmol/L; and 72 hours after dosage, the concentration should be <0.1 mcmol/L or <0.05 mcmol/L, depending on clinical protocol. It is also administered at low dose (a single dose of 5-15 mg per week) to treat severe psoriasis and rheumatoid arthritis. Methotrexate is 65% orally bioavailable. Peak serum concentrations are reached 2 to 3 hours after dosing. Protein binding is approximately 45%. Volume of distribution is 0.4 L/kg. Elimination is concentration dependent with an apparent elimination half-life of 1.8 hours when the serum concentration is >1 mcmol/L, 8 hours when between 0.1 and 1 mcmol/L, and approximately 30 hours when <0.1 mcmol/L. Voraxaze (glucarpidase) is a carboxypeptidase enzyme indicated for the treatment of toxic plasma methotrexate (MTX) concentrations (>1 mcmol/L) in patients with delayed methotrexate clearance due to impaired renal function. Measurement of methotrexate using immunoassays is unreliable for specimens collected within 48 hours following Voraxaze administration since it can result in falsely elevated results. As a result, this liquid chromatography-tandem mass spectrometry assay should be used to monitor MTX concentrations postglucarpidase therapy.

**Useful For:** Monitoring methotrexate concentrations postglucarpidase therapy

**Interpretation:** Following a 4 to 6 hour intravenous infusion of methotrexate, postinfusion concentrations greater than the following indicate an increased risk of toxicity if conventional low-dose leucovorin rescue is given: 24-hour postinfusion concentration: 5.0 to 10.0 mcmol/L - 48-hour postinfusion concentration: 0.5 to 1.0 mcmol/L - 72-hour postinfusion concentration: 0.1 mcmol/L

**Reference Values:**
Nontoxic drug concentration after 72 hours: <0.1 mcmol/L

**Clinical References:** Cadman EC, Durivage HJ: Cancer chemotherapy: alkylating agents. In Harrison's Principles of Internal Medicine. 12th edition. Edited by JD Wilson, E Braunwald, KJ
Methotrexate, Serum

Clinical Information: Methotrexate is an antineoplastic agent that inhibits DNA synthesis. The drug exerts its effects through competitive inhibition of the enzyme dihydrofolate reductase thus decreasing the concentrations of tetrahydrofolate essential to the methylation of pyrimidine nucleotides and consequently the rate of pyrimidine nucleotide and ultimately DNA synthesis. Methotrexate is used in the treatment of certain neoplastic diseases, severe psoriasis, and adult rheumatoid arthritis. Methotrexate is effective against malignancies characterized by rapid cell proliferation. Intermediate to high doses of methotrexate with leucovorin (citrovorum-factor or folinic acid) rescue to salvage nontumor cells have been used with favorable results in the treatment of osteogenic sarcoma, leukemia, non-Hodgkin lymphoma, lung, and breast cancer. Methotrexate has the potential for serious toxicity. Patients undergoing methotrexate therapy are closely monitored so that toxic effects are detected promptly.

Useful For: Following therapy, serum concentration is used to judge whether the drug is being cleared appropriately and verify that a nontoxic concentration has been attained.

Interpretation: Serum concentrations of methotrexate are commonly monitored during high-dose therapy (>50 mg/m²) to identify the time at which active intervention by leucovorin rescue should be initiated. Criteria for serum concentrations indicative of a potential for toxicity after single-bolus, high-dose therapy are as follows: -Methotrexate >10 mcmol/L 24 hours after dose -Methotrexate >1 mcmol/L 48 hours after dose -Methotrexate >0.1 mcmol/L 72 hours after dose

Reference Values:
Nontoxic drug concentration after 72 hours: <0.1 mcmol/L.


Methsuximide (Celontin) as Desmethylmethsuximide

Reference Values:
10.0 - 40.0 ug/mL

Methsuximide measured as desmethylmethsuximide.

Methylmalonic Acid (MMA), Amniotic Fluid

Clinical Information: Methylmalonic acid (MMA) is a specific diagnostic marker for the group of disorders collectively called methylmalonic acidemia, which includes at least 7 different complementation groups. Two of them (mut0 and mut-) reflect deficiencies of the apoenzyme portion of the enzyme methylmalonyl-CoA mutase. Two other disorders (CblA and CblB) are associated with abnormalities in the adenosylcobalamin synthesis pathway. CblC, CblD, and CblF deficiencies lead to impaired synthesis of both adenosyl- and methylcobalamin. Since the first reports of this disorder in 1967, thousands of cases have been diagnosed worldwide. Newborn screening identifies approximately 1 in 30,000 live births with a methylmalonic acidemia. The most frequent clinical manifestations are neonatal or infantile metabolic ketoacidosis, failure to thrive, and developmental delay. Excessive protein intake may cause life-threatening episodes of metabolic decompensation and remains a lifelong risk unless treatment is closely monitored, including serum and urine MMA levels. Because the morbidity and mortality of methylmalonic acidemia are high, genetic counseling and prenatal diagnosis are frequently sought by families with 1 or more affected children. The prenatal diagnosis is made on a dual, complementary
approach: enzymatic assays in cultured amniocytes or molecular analysis for previously identified familial mutations and direct chemical determination of MMA in cell-free supernatant of amniotic fluid from amniocentesis between 16 and 19 weeks of gestational age.

**Useful For:** Specific prenatal diagnostic marker for methylmalonic acidemia

**Interpretation:** A significantly increased amniotic fluid methylmalonic acid concentration supports a diagnosis of methylmalonic acidemia.

**Reference Values:**
<1.50 nmol/mL

**Clinical References:**

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**Methylmalonic Acid (MMA), Quantitative, Plasma**

**Clinical Information:** Elevated levels of methylmalonic acid (MMA) result from inherited defects of enzymes involved in MMA metabolism or inherited or acquired deficiencies of vitamin B12 or its downstream metabolites. Of the 2, nutritional deficiencies are much more common and can be due to intestinal malabsorption, impaired digestion, or poor diet. Elderly patients with cobalamin deficiency may present with peripheral neuropathy, ataxia, loss of position and vibration senses, memory impairment, depression, and dementia in the absence of anemia. Other conditions such as renal insufficiency, hypovolemia, and bacterial overgrowth of the small intestine also contribute to the possible causes of mild methylmalonic acidemia and aciduria. MMA is also a specific diagnostic marker for the group of disorders collectively called methylmalonic acidemia, which include at least 7 different complementation groups. Two of them (mut0 and mut-) reflect deficiencies of the apoenzyme portion of the enzyme methylmalonyl-CoA mutase. Two other disorders (CblA and CblB) are associated with abnormalities of the adenosylcobalamin synthesis pathway. CblC, CblD, and CblF deficiencies lead to impaired synthesis of both adenosyl- and methylcobalamin. Since the first reports of this disorder in 1967, many hundreds of cases have been diagnosed worldwide. Newborn screening identifies approximately 1 in 30,000 live births with a methylmalonic acidemia. The most frequent clinical manifestations are neonatal or infantile metabolic ketoacidosis, failure to thrive, and developmental delay. Excessive protein intake may cause life-threatening episodes of metabolic decompensation and remains a life-long risk unless treatment is closely monitored, including plasma and urine MMA levels. Several studies have suggested that the determination of plasma or urinary methylmalonic acid could be a more reliable marker of cobalamin deficiency than direct cobalamin determination.

**Useful For:** Evaluating children with signs and symptoms of methylmalonic acidemia Evaluating individuals with signs and symptoms associated with a variety of causes of cobalamin (vitamin B12) deficiency

**Interpretation:** In pediatric patients, markedly elevated methylmalonic acid values indicate a probable diagnosis of methylmalonic acidemia. Additional confirmatory testing must be performed. In adults, moderately elevated values indicate a likely cobalamin deficiency.

**Reference Values:**
< or =0.40 nmol/mL

**Methylmalonic Acid (MMA), Quantitative, Serum**

**Clinical Information:** Elevated levels of methylmalonic acid (MMA) result from inherited defects of enzymes involved in MMA metabolism or inherited or acquired deficiencies of vitamin B12 (cobalamin) or its downstream metabolites. Acquired nutritional deficiencies are much more common than inherited defects and can be due to intestinal malabsorption, impaired digestion, or poor diet. Elderly patients with cobalamin deficiency may present with peripheral neuropathy, ataxia, loss of position and vibration senses, memory impairment, depression, and dementia in the absence of anemia. Other conditions such as renal insufficiency, hypovolemia, and bacterial overgrowth of the small intestine also contribute to the possible causes of mild methylmalonic acidemia and aciduria. MMA is also a specific diagnostic marker for the group of disorders collectively called methylmalonic acidemia, which include at least 7 different complementation groups. Two of them (mut0 and mut-) reflect deficiencies of the apoenzyme portion of the enzyme methylmalonyl-CoA mutase. Two other disorders (CblA and CblB) are associated with abnormalities of the adenosylcobalamin synthesis pathway. CblC, CblD, and CblF deficiencies lead to impaired synthesis of both adenosyl- and methylcobalamin. Since the first reports of this disorder in 1967, thousands of cases have been diagnosed worldwide. Newborn screening identifies approximately 1 in 30,000 live births with a methylmalonic acidemia. The most frequent clinical manifestations are neonatal or infantile metabolic ketoacidosis, failure to thrive, and developmental delay. Excessive protein intake may cause life-threatening episodes of metabolic decompensation and remains a lifelong risk unless treatment is closely monitored, including serum and urine MMA levels. Several studies have suggested that the determination of serum or urinary methylmalonic acid could be a more reliable marker of cobalamin deficiency than direct cobalamin determination.

**Useful For:** Evaluating children with signs and symptoms of methylmalonic acidemia Evaluating individuals with signs and symptoms associated with a variety of causes of cobalamin (vitamin B12) deficiency

**Interpretation:** In pediatric patients, markedly elevated methylmalonic acid values indicate a probable diagnosis of methylmalonic acidemia. Additional confirmatory testing must be performed. In adults, moderately elevated values indicate a likely cobalamin (vitamin B12) deficiency.

**Reference Values:**
< or =0.40 nmol/mL


**Methylmalonic Acid (MMA), Quantitative, Urine**

**Clinical Information:** Elevated levels of methylmalonic acid (MMA) result from inherited defects of enzymes involved in MMA metabolism or inherited or acquired deficiencies of vitamin B12 (cobalamin) or its downstream metabolites. Acquired nutritional deficiencies are much more common than inherited defects and can be due to intestinal malabsorption, impaired digestion, or poor diet. Elderly patients with cobalamin deficiency may present with peripheral neuropathy, ataxia, loss of position and vibration senses, memory impairment, depression, and dementia in the absence of anemia. Other conditions such as renal insufficiency, hypovolemia, and bacterial overgrowth of the small intestine also contribute to the possible causes of mild methylmalonic acidemia and aciduria. MMA is also a specific diagnostic marker for the group of disorders collectively called methylmalonic acidemia, which include at least 7 different complementation groups. Two of them (mut0 and mut-) reflect deficiencies of the apoenzyme portion of the enzyme methylmalonyl-CoA mutase. Two other disorders (CblA and CblB) are associated with abnormalities of the adenosylcobalamin synthesis pathway. CblC, CblD, and CblF deficiencies lead to impaired synthesis of both adenosyl- and methylcobalamin. Since the first reports of this disorder in 1967, thousands of cases have been diagnosed worldwide. Newborn screening identifies approximately 1 in 30,000 live births with a methylmalonic acidemia. The most frequent clinical manifestations are neonatal or infantile metabolic ketoacidosis, failure to thrive, and developmental delay. Excessive protein intake may cause life-threatening episodes of metabolic decompensation and remains a lifelong risk unless treatment is closely monitored, including serum and urine MMA levels. Several studies have suggested that the determination of serum or urinary methylmalonic acid could be a more reliable marker of cobalamin deficiency than direct cobalamin determination.

**Useful For:** Evaluating children with signs and symptoms of methylmalonic acidemia Evaluating individuals with signs and symptoms associated with a variety of causes of cobalamin (vitamin B12) deficiency

**Interpretation:** In pediatric patients, markedly elevated methylmalonic acid values indicate a probable diagnosis of methylmalonic acidemia. Additional confirmatory testing must be performed. In adults, moderately elevated values indicate a likely cobalamin (vitamin B12) deficiency.

**Reference Values:**
< or =0.40 nmol/mL

Clinical Information: Elevated levels of methylmalonic acid (MMA) result from inherited defects of enzymes involved in MMA metabolism or inherited or acquired deficiencies of vitamin B12 or its downstream metabolites. Of the 2, nutritional deficiencies are much more common and can be due to intestinal malabsorption, impaired digestion, or poor diet. Elderly patients with cobalamin deficiency may present with peripheral neuropathy, ataxia, loss of position and vibration senses, memory impairment, depression, and dementia in the absence of anemia. Other conditions such as renal insufficiency, hypovolemia, and bacterial overgrowth of the small intestine also contribute to the possible causes of mild methylmalonic acidemia and aciduria. MMA is also a specific diagnostic marker for the group of disorders collectively called methylmalonic acidemia, which include at least 7 different complementation groups. Two of them (mut0 and mut-) reflect deficiencies of the apoenzyme portion of the enzyme methylmalonyl-CoA mutase. Two other disorders (CblA and CblB) are associated with abnormalities of the adenosylcobalamin synthesis pathway. CblC, CblD, and CblF deficiencies lead to impaired synthesis of both adenosyl- and methylcobalamin. Since the first reports of this disorder in 1967, many hundreds of cases have been diagnosed worldwide. Newborn screening identifies approximately 1 in 30,000 live births with a methylmalonic acidemia. The most frequent clinical manifestations are neonatal or infantile metabolic ketoacidosis, failure to thrive, and developmental delay. Excessive protein intake may cause life-threatening episodes of metabolic decompensation and remains a life-long risk unless treatment is closely monitored, which includes serum and urine MMA levels. Several studies have suggested that the determination of serum or urinary methylmalonic acid could be a more reliable marker of cobalamin deficiency than direct cobalamin determination.

Useful For: Evaluating children with signs and symptoms of methylmalonic acidemia Evaluating individuals with signs and symptoms associated with a variety of causes of cobalamin deficiency

Interpretation: In pediatric patients, markedly elevated methylmalonic acid values indicate a probable diagnosis of methylmalonic acidemia. Additional confirmatory testing must be performed. In adults, moderately elevated values indicate a likely cobalamin deficiency.

Reference Values: <3.60 mmol/mol creatinine


Methylmalonic Aciduria and Homocystinuria, cblC Type, Full Gene Analysis

Clinical Information: Multiple causes of inborn errors of cobalamin (cbl; better known as vitamin B12) metabolism have been identified. These disorders have been classified into 9 distinct complementation classes (cblA-cblH and mut, caused by mutations in the gene encoding methylmalonyl coenzyme A mutase). Complementation analysis utilizes cells from the patient to determine at what stage of the cbl metabolism pathway an error is occurring, and uses this information to differentiate between the various complementation class disorders. Depending on the complementation class involved, errors in cbl metabolism can result in methylmalonic aciduria, homocystinuria, or both. The most common disorder in this group is methylmalonic aciduria and homocystinuria, cblC (cobalamin C) type, which results in both methylmalonic aciduria and homocystinuria. cblC type is an autosomal recessive disorder with a variable age of onset. In the early onset form, symptoms appear in the first several years of life and include failure to thrive, developmental delay, seizures, metabolic crisis, and hydrocephalus. Patients may also have hemolytic uremic syndrome. Adults can present with confusion
or other changes in mental status, cognitive decline, and megaloblastic anemia. Biochemical presentation includes methylmalonic aciduria and homocystinuria in urine organic acid or plasma amino acid analysis. Other complementation class disorders, such as cblD and cblF, can result in a similar biochemical phenotype, and complementation testing or molecular testing is utilized to distinguish between these different types. Mutations in the MMACHC gene are responsible for the cblC type disorder. The most common mutation (identified in approximately 40% of mutant alleles) is 271dupA. This multiethnic mutation is most frequently associated with early-onset disease, especially when present in the homozygous state. Another early-onset mutation is R111X, which is common in the Cajun and French Canadian populations. R132X is a late-onset mutation that has been identified in individuals of Indian, Pakistani, and Middle Eastern ethnicity. Although these genotype-phenotype correlations are well-established, there is often considerable variability in age of onset and expression of symptoms, even within families.

**Useful For:** Confirmation of diagnosis of methylmalonic aciduria and homocystinuria, cblC type Distinguishing between cblC, cblD, and cblF types when methylmalonic aciduria and homocystinuria are identified Carrier screening in cases where there is a family history of methylmalonic aciduria and homocystinuria, but disease-causing mutations have not been identified in an affected individual

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Methylmalonic Aciduria and Homocystinuria, cblD Type, Full Gene Analysis**

**Clinical Information:** Several causes of inborn errors of cobalamin (cbl; better known as vitamin B12) metabolism have been identified. These disorders have been classified into 8 distinct complementation classes (cblA-cblH). Complementation analysis utilizes cells from the patient to determine at what stage of the cbl metabolism pathway an error is occurring, and uses this information to differentiate between the various complementation class disorders. Depending on the complementation class involved, errors in cbl metabolism can result in methylmalonic aciduria, homocystinuria, or both. cblD type is a rare autosomal recessive disorder with variable clinical presentations. It can present as cblD variant 1, associated with isolated homocystinuria; cblD variant 2, associated with isolated methylmalonic aciduria; or as cblD combined, associated with both methylmalonic aciduria and homocystinuria. cblD variant 1 is associated with clinical features of isolated homocystinuria, including megaloblastic anemia and neurological abnormalities, as well as developmental delays. cblD variant 2 is associated with clinical features of isolated methylmalonic aciduria, including metabolic decomposition, which can result in lethargy, failure to thrive, feeding problems, and hypotonia. cblD combined is associated with clinical features of both methylmalonic aciduria and homocystinuria. Biochemical presentation includes methylmalonic aciduria and/or homocystinuria in urine organic acid or plasma amino acid analysis.(1) Other complementation class disorders can result in a similar biochemical phenotype, and complementation testing or molecular testing is utilized to distinguish between these different types. Mutations in the MMADHC gene are responsible for the cblD type disorder. To date, 9 mutations in 7 individuals have been identified.(2) Three missense mutations identified in exons 6 and 8 have been

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**MHDZ**

35490
associated with cblD variant 1. One nonsense mutation, 1 in-frame duplication, and 1 frame-shift deletion in exons 3 and 4 have been associated with cblD variant 2. One nonsense mutation, 1 frame-shift duplication, and 1 splice-site deletion in exons 5 and 8 and intron 7 have been associated with cblD combined.

**Useful For:** Confirmation of diagnosis of disorders belonging to the cblD complementation group Distinguishing between cblC, cblD, and cblF types when methylmalonic aciduria and homocystinuria are identified Distinguishing between cblA, cblB, and cblD variant 2 when methylmalonic aciduria is identified Distinguishing between cblD variant 1, cblE, and cblG when homocystinuria is identified Carrier screening in cases where there is a family history of methylmalonic aciduria or homocystinuria, but disease-causing mutations have not been identified in an affected individual

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.


**FMMTU**  
Methylphenidate (Ritalin) & MTB, Urine  
**Reference Values:**  
Reference Range: Not Established  
Units: ng/mL

**RIT**  
Methylphenidate, Serum  
**Reference Values:**  
Reference Range: 5.0 - 20.0 ng/mL

**MEX**  
Mexiletine, Serum  
**Clinical Information:** Mexiletine is a class I B antiarrhythmic with electrophysiologic properties similar to lidocaine and is useful in suppression of ventricular arrhythmias. The drug exhibits a high degree of oral bioavailability, is approximately 60% protein bound, and undergoes renal clearance at a rate of 10.3 mL/min/kg. Mexiletine has a volume of distribution of 9.5 L/kg at a half-life of 11 hours. Myocardial infarction and uremia reduce the rate of clearance and increase the half-life of mexiletine, requiring dosage adjustment guided by drug monitoring. Mexiletine toxicity occurs at concentrations >2.0 mcg/mL (trough value) and is characterized by symptoms of nausea, hypotension, sinus bradycardia, paresthesia, seizures, intermittent left bundle branch block, and temporary asystole.

**Useful For:** Assessing achievement of optimal therapeutic concentrations Assessing potential toxicity

**Interpretation:** Optimal response to mexiletine occurs when the serum concentration is within the
range of 0.8 to 2.0 mcg/mL (trough value).

Reference Values:
Therapeutic concentration: 0.8-2.0 mcg/mL (trough value)
Toxic concentration: >2.0 mcg/mL (trough value)

Clinical References:

MGMT Promoter Methylation, Tumor

Clinical Information: Glioblastoma (WHO grade IV astrocytoma) is the most frequent malignant primary central nervous system tumor in adults. It has a very poor prognosis, with median survival of less than a year. Current standard of care consists of surgical resection followed by radiotherapy in addition to alkylating chemotherapy with temozolomide. MGMT (O[6]-methylguanine-DNA methyltransferase) is a DNA repair enzyme. This enzyme rescues tumor cells from alkylating agent-induced damage, and this leads to resistance to chemotherapy with alkylating agents. Epigenetic silencing of the MGMT gene by promoter methylation results in decreased MGMT protein expression, reduced DNA repair activity, and potential increased sensitivity to therapy. MGMT promoter methylation status has been most widely evaluated by methylation-specific PCR method, which is both sensitive and specific. In newly diagnosed glioblastomas, the presence of MGMT promoter methylation has been shown to be an independent favorable prognostic factor and a strong predictor of responsiveness to alkylating chemotherapy (ie, temozolomide). This is particularly relevant for elderly patients (>60 years), who usually have decreased tolerance for combined aggressive chemoradiation. For this group of patients, recent clinical trials have provided strong evidence supporting an alternative therapeutic strategy consisting of monotherapy with the alkylating agent temozolomide for patients whose tumors show MGMT promoter methylation and radiotherapy alone for patients whose tumors lack MGMT promoter methylation. Thus, in addition to the significant prognostic and predictive value, MGMT methylation status has emerged as a valuable biomarker to guide therapy decision making for newly diagnosed glioblastoma in elderly patients, preventing unnecessary treatment toxicities and costs. MGMT promoter methylation has been reported to high rates in oligodendrogliomas and astrocytomas of lower grade, in which they variably correlate with 1p19q codeletion and IDH mutations. Prognostic and predictive significance of MGMT promoter methylation status in these tumors has been shown in some studies, but not in others.

Useful For: Prognostication of newly diagnosed glioblastomas Identifying newly diagnosed glioblastomas that may respond to alkylating chemotherapy (ie, temozolomide) Guiding therapy decision making for newly diagnosed glioblastomas in elderly patients (>60 years)

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.

Clinical References:
**Clinical Information:**

**Interpretation:** MI-2 is a Myositis specific Autoantibody and is seen in 5-10% of adult Dermatomyositis and in 5% of Juvenile Dermatomyositis cases.

**Reference Values:**
Negative

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**Microalbumin, Random, Urine**

**Clinical Information:** Diabetic nephropathy is a complication of diabetes and is characterized by proteinuria (normal urinary albumin excretion is <30 mg/day; overt proteinuria is >300 mg/day). Before overt proteinuria develops, albumin excretion increases in those diabetic patients who are destined to develop diabetic nephropathy. Therapeutic maneuvers (eg, aggressive blood pressure maintenance, particularly with angiotensin-converting enzyme inhibitors; aggressive blood sugar control; and possibly decreased protein intake) can significantly delay, or possibly prevent, development of nephropathy. Thus, there is a need to identify small, but abnormal, increases in the excretion of urinary albumin (in the range of 30-300 mg/day, ie, microalbuminuria). The National Kidney Foundation guidelines for the management of patients with diabetes and microalbuminuria recommend that all type 1 diabetic patients older than 12 years and all type 2 diabetic patients younger than 70 years have their urine tested for microalbuminuria yearly when they are under stable glucose control.(1) The preferred specimen is a 24-hour collection, but a random collection is acceptable. Studies have shown that correcting albumin for creatinine excretion rates has similar discriminatory value with respect to diabetic renal involvement. The albumin:creatinine ratio from a random urine specimen is also considered a valid screening tool.(2) Several studies have addressed whether the specimen needs to be a fasting urine, an exercised urine, or an overnight urine specimen. These studies have shown that the first-morning urine specimen is less sensitive, but more specific. Studies also have shown that microalbuminuria is a marker of generalized vascular disease and is associated with stroke and heart disease.

**Useful For:** Assessing the potential for early onset of nephropathy in diabetic patients

**Interpretation:** In random urine specimens, normal urinary albumin excretion is below 17 mg/g creatinine for males and below 25 mg/g creatinine for females.(3) Microalbuminuria is defined as an albumin:creatinine ratio of 17 to 299 for males and 25 to 299 for females. A ratio of albumin:creatinine of 300 or higher is indicative of overt proteinuria. Due to biologic variability, positive results should be confirmed by a second, first-morning random or 24-hour timed urine specimen. If there is discrepancy, a third specimen is recommended. When 2 out of 3 results are in the microalbuminuria range, this is evidence for incipient nephropathy and warrants increased efforts at glucose control, blood pressure control, and institution of therapy with an ACE inhibitor (if the patient can tolerate it).

**Reference Values:**
Males: <17 mg/g creatinine
Females: <25 mg/g creatinine


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**Microalbuminuria, 24 Hour, Urine**

**Clinical Information:** Albumin excretion increases in patients with diabetes who are destined to develop overt diabetic nephropathy. Microalbuminuria (an albumin:creatinine ratio of 17 to 299 mg/g) is often the earliest sign of renal involvement and may precede microalbuminuria by many years. Microalbuminuria has been shown to be associated with a number of cardiovascular events (including stroke and heart disease). The National Kidney Foundation guidelines recommend that all type 1 diabetic patients older than 12 years and all type 2 diabetic patients younger than 70 years have their urine tested for microalbuminuria yearly when they are under stable glucose control.

**Useful For:** Assessing the potential for early onset of nephropathy in diabetic patients

**Interpretation:** In 24-hour urine specimens, normal urinary albumin excretion is below 17 mg/g creatinine for males and below 25 mg/g creatinine for females.(3) Microalbuminuria is defined as an albumin:creatinine ratio of 17 to 299 for males and 25 to 299 for females. A ratio of albumin:creatinine of 300 or higher is indicative of overt proteinuria. Due to biologic variability, positive results should be confirmed by a second, 24-hour random or timed urine specimen. If there is discrepancy, a third specimen is recommended. When 2 out of 3 results are in the microalbuminuria range, this is evidence for incipient nephropathy and warrants increased efforts at glucose control, blood pressure control, and institution of therapy with an ACE inhibitor (if the patient can tolerate it).

**Reference Values:**
Males: <17 mg/g creatinine
Females: <25 mg/g creatinine

develop diabetic nephropathy. More importantly, at this phase of increased albumin excretion before overt proteinuria develops, therapeutic maneuvers can be expected to significantly delay, or possibly prevent, development of nephropathy. These maneuvers include aggressive blood pressure maintenance (particularly with angiotensin-converting enzyme inhibitors), aggressive blood sugar control, and possibly decreased protein intake. Thus, there is a need for addressing small amounts of urinary albumin excretion (in the range of 30-300 mg/day, ie, microalbuminuria). The National Kidney Foundation convened an expert panel to recommend guidelines for the management of patients with diabetes and microalbuminuria. These guidelines recommend that all type 1 diabetic patients older than 12 years and all type 2 diabetic patients younger than 70 years should have their urine tested for microalbuminuria yearly when they are under stable glucose control.(1) The preferred specimen is a 24-hour collection, but a 10-hour overnight collection (9 p.m. to 7 a.m.) or a random collection are acceptable. Recent studies have shown that correcting albumin for creatinine excretion rates has similar discriminatory value with respect to diabetic renal involvement, and it is now suggested that an albumin/creatinine ratio from a random urine specimen is a valid screening tool.(2) Several studies have addressed the question of whether this needs to be a fasting urine, an exercised urine, or an overnight urine specimen. From these studies, it is clear that the first-morning urine specimen is less sensitive, but more specific. A positive result should be confirmed by a first-morning random or 24-hour timed urine specimen. Studies have also shown that microalbuminuria is a marker of generalized vascular disease and is associated with stroke and heart disease.

**Useful For:** Evaluating diabetic patients to assess the potential for early onset of nephropathy

**Interpretation:** An albumin excretion rate >30 mg/24 hours is considered to be microalbuminuric. By definition, the upper end of microalbuminuria is thought to be 300 mg/24 hours. Although this level has not been rigorously defined, it is felt that at this level it is more difficult to change the course of diabetic nephropathy. We have established normal values in our laboratory and agree with the 30 mg/24 hour level. A normal excretion rate of 20 mcg/minute has also been established in the literature and is consistent with our data. Thus, microalbuminuria has been defined at 30 to 300 mg/24 hours. The literature has defined the albumin/creatinine ratio (mg/g) <17 as normal for males and <25 for females(2) and is consistent with our normal data. A ratio of albumin to creatinine of > or =300 indicates overt albuminuria. Thus, microalbuminuria has been defined as an albumin/creatinine ratio of 17 to 299 for males and 25 to 299 for females. Due to biologic variability, any patient who has an albumin/creatinine ratio or urinary albumin excretion rate in the positive microalbuminuria range should have this confirmed with a second specimen. If there is discrepancy, a third specimen is recommended. If 2 of 3 results are in the positive microalbuminuria range, this is evidence for incipient nephropathy and warrants increased efforts at glucose control, aggressive blood pressure control, and institution of therapy with an angiotensin-converting enzyme inhibitor (if the patient can tolerate it).

**Reference Values:**
24-Hour excretion: <30 mg/24 hours
Excretion rate: <20 mcg/min

**Clinical References:**

MLCPC 113370  
**Microdissection, Laser Capture (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.
**Micropolyspora faeni, IgG Antibodies, Serum**

**Clinical Information:** Micropolyspora faeni is one of the causative agents of hypersensitivity pneumonitis (HP). Other causative microorganisms include Thermoactinomyces vulgaris and Aspergillus fumigatus. The development of HP caused by Micropolyspora faeni is accompanied by an immune response to Micropolyspora faeni antigens with production of IgG antibodies. While the immunopathogenesis of HP is not known, several immune mechanisms are postulated to play a role, including both cellular and humoral mechanisms.(1)

**Useful For:** Evaluation of patients suspected of having hypersensitivity pneumonitis induced by exposure to Micropolyspora faeni

**Interpretation:** Elevated concentrations of IgG antibodies to Micropolyspora faeni, Thermoactinomyces vulgaris, or Aspergillus fumigatus in patients with signs and symptoms of hypersensitivity pneumonitis may be consistent with disease caused by exposure to 1 or more of these organic antigens.

**Reference Values:**
- 0-12 years: < or =4.9 mg/L
- 13-18 years: < or =9.1 mg/L
- >18 years: < or =13.2 mg/L

**Clinical References:**

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**Microsatellite Instability (MSI), Tumor**

**Clinical Information:** Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3-prime end of the EPCAM gene have also been associated with HNPCC/Lynch syndrome, as this leads to inactivation of the MSH2 promoter. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome related genes and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are less than 15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described but also include brain and central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous mismatch repair mutations, characterized by the presence of bi-allelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of HNPCC/Lynch syndrome. Tumors from individuals with HNPCC/Lynch syndrome demonstrate microsatellite instability (MSI), characterized by numerous alterations in a type of repetitive DNA called microsatellites. Two distinct MSI tumor phenotypes have been described: MSI-H (instability in >30% of microsatellites examined) and MSS/MSI-L (instability in <30% of microsatellites examined). The MSI-H phenotype is associated with germline defects in the MLH1, MSH2, MSH6, or PMS2 genes, and is the primary phenotype observed.
in tumors from patients with HNPCC/Lynch syndrome. Immunohistochemistry (IHC) is a complementary testing strategy to MSI testing. Most MSI-H tumors show a loss of protein expression for at least 1 of the 4 mismatch repair genes described above. Loss of expression of proteins within the tumor is helpful in identifying which corresponding genes to target for mutation analysis. Although MSI and IHC are best interpreted together, they are also available separately to accommodate clinical situations in which there are barriers to performing these tests concurrently (eg, financial concerns, specimen requirements). Testing is typically first performed on the tumor of an affected individual and in the context of other risk factors, such as young age at diagnosis or a strong family history of colon cancer or other HNPCC/Lynch syndrome-related cancers. If defective DNA mismatch repair is identified within the tumor, mutation analysis of the associated gene can be performed to identify the causative germline mutation and allow for predictive testing of at-risk individuals. Of note, MSI-H phenotypes and loss of protein expression by IHC have also been demonstrated in various sporadic cancers, including those of the colon and endometrium. Absence of MLH1 and PMS2 protein expression within a tumor, for instance, is most often associated with a somatic alteration in individuals with an older age of onset of cancer than typical HNPCC/Lynch syndrome families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between somatic and germline mutations. Genetic testing of the gene indicated by IHC analysis can help to distinguish between these 2 possibilities. In addition, when absence of MLH1/PMS2 is observed, BRMLH / MLH1 Hypermethylation and BRAF Mutation Analysis, Tumor or ML1HM / MLH1 Hypermethylation Analysis, Tumor may also help to distinguish between a sporadic and germline etiology. It should be noted that MSI testing is not a genetic test, but rather helps to stratify the risk of having an inherited cancer predisposition syndrome, and identifies patients who might benefit from subsequent genetic testing. Immunohistochemistry is available as an add-on to this test (IHC / Mismatch Repair [MMR] Protein Immunohistochemistry Only, Tumor). If both MSI and IHC are desired, please order the profile test, HNPCC screen (MSIHC / Microsatellite Instability [MSI]/Immunohistochemistry [IHC] Profile; Lynch/Hereditary Nonpolyposis Colorectal Cancer [HNPCC] Screen). See Lynch Syndrome Testing Algorithm in Special Instructions for additional information. Evaluation for MSI may also be valuable for clinical decision making. Colon cancers that demonstrate defective DNA mismatch repair (MSI-H) have a significantly better prognosis compared to those with intact mismatch repair (MSS/MSI-L). Additionally, current data indicate that stage II and stage III patients with colon cancers characterized by the presence of defective MMR (MSI-H) may not benefit from treatment with fluorouracil (5-FU) alone or in combination with leucovorin (LV). These findings are most likely to impact the management of patients with stage II disease.

**Useful For:** Evaluation through comparison of both tumor and normal tissue to identify patients at high risk for having hereditary nonpolyposis colorectal cancer (HNPCC)/Lynch syndrome Evaluation through comparison of both tumor and normal tissue for clinical decision-making purposes given the prognostic implications associated with MSI phenotypes This test cannot be used to assess tumor tissue unless both tumor and normal tissue are submitted.

**Interpretation:** The report will include specimen information, assay information, and interpretation of test results. Microsatellite stable (MSS) is reported as MSS/MSI-L (0 or 1 of 5 markers demonstrating instability) or MSI-H (2 or more of 5 markers demonstrating instability).

**Reference Values:** An interpretive report will be provided.

Microsatellite Instability (MSI)/Mismatch Repair (MMR) Protein Immunohistochemistry Profile

Clinical Information: Assessment for defective mismatch repair (dMMR) through microsatellite instability (MSI) and immunohistochemistry (IHC) analysis is a predictor of therapeutic response in solid tumors. Current data suggest that unresectable or metastatic solid tumors with microsatellite instability-high (MSI-H) or defective mismatch repair (dMMR) may respond to anti-PD-L1/PD-1 immunotherapy (eg, pembrolizumab). Colon cancers that demonstrate defective DNA mismatch repair (MSI-H) have a significantly better prognosis compared to those with intact mismatch repair (MSS/MSI-L). Additionally, current data indicate that stage II patients with colon cancers characterized by the presence of defective MMR (MSI-H) may not benefit from treatment with fluorouracil (5-FU) alone or in combination with leucovorin (LV). Additionally, assessment for dMMR in tumors has utility in evaluating patients for Lynch syndrome. Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPPC), is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3-prime end of the EPCAM gene have also been associated with HNPPC/Lynch syndrome, as this leads to inactivation of the MSH2 promoter. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome-related genes and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are less than 15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozgyous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described but also include brain and central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of HNPPC/Lynch syndrome. Testing tumors from individuals at risk for HNPPC/Lynch syndrome for microsatellite instability (MSI) indicates the presence or absence of defective DNA mismatch repair within the tumor. Individuals whose tumors demonstrate the presence of defective DNA mismatch repair in the form of microsatellite instability are more likely to have a germline mutation in 1 of the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Tumors from affected individuals usually demonstrate an MSI-H phenotype (MSI >30% of microsatellites examined), whereas tumors from individuals who do not have HNPPC/Lynch syndrome usually have an MSS/MSI-L phenotype (MSI at <30% of microsatellites examined). Immunohistochemistry (IHC) is a complementary testing strategy to MSI testing. In addition to identifying tumors with defective DNA mismatch repair, IHC analysis is helpful for identifying the gene responsible for the defective DNA mismatch repair within the tumor, because the majority of MSI-H tumors show a loss of expression of at least 1 of the 4 mismatch repair genes described above. Testing is typically first performed on the tumor of an affected individual and in the context of other risk factors, such as young age at diagnosis or a strong family history of HNPPC/Lynch syndrome-related cancers. If defective DNA mismatch repair is identified within the tumor, mutation analysis of the associated gene can be performed to identify the causative germline mutation and allow for predictive testing of at-risk individuals. Of note, MSI-H phenotypes and loss of protein expression by IHC have also been demonstrated in various sporadic cancers, including those of the colon and endometrium. Absence of MLH1 and PMS2 protein expression within a tumor, for instance, is most often associated with a somatic alteration in individuals with an older age of onset of cancer than typical HNPPC/Lynch syndrome families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between somatic and germline mutations. Genetic testing of the gene indicated by IHC analysis can help to distinguish between these 2...
possibilities. In addition, when absence of MLH1/PMS2 is observed, BRMLH / MLH1
Hypermethylation and BRAF Mutation Analysis, Tumor or ML1HM / MLH1 Hypermethylation
Analysis, Tumor may also help to distinguish between a sporadic and germline etiology. It should be
noted that this test is not a genetic test, but rather stratifies the risk of having an inherited cancer
predisposition syndrome, and identifies patients who might benefit from subsequent genetic testing. See
Hereditary Nonpolyposis Colorectal Cancer Testing Algorithm in Special Instructions for additional
information.

**Useful For:** Assessment for defective mismatch repair (dMMR) to identify solid tumors that may
respond to anti-PD-L1/PD-1 immunotherapy Evaluation of colon tumor tissue for evidence of
microsatellite instability to stratify prognosis Identification of individuals at high risk for having
hereditary nonpolyposis colorectal cancer (HNPCC)/Lynch syndrome

**Interpretation:** The report will include specimen information, assay information, and interpretation of
test results. Microsatellite stable (MSS) is reported as MSS/MSI-L (0 or 1 of 5 markers demonstrating
instability) or MSI-H (2 or more of 5 markers demonstrating instability).

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
1. Baudhuin LM, Burgart LJ, Leontovich O, Thibodeau SN: Use of
microsatellite instability and immunohistochemistry testing for the identification of individuals at risk for
detection of hereditary nonpolyposis colorectal cancer gene carriers by screening for tumor microsatellite
instability before germline genetic testing. Gastroenterology 2001 January;120(1):21-30 3. Vasen HF,
GeneReviews 2004 Feb 5 (Updated 2014 May 22) edited by RA Pagon, MP Adam, HH Ardinger, et al:
Seattle WA. University of Washington, Seattle; 1993-2014. Available at
microsatellite instability and colorectal cancer prognosis. JCO 2005 23(3):609-618 6. Ribic CM, Sargent
DJ, Moore MJ, et al: Tumor microsatellite-instability status as a predictor of benefit from
2015 25;372(26):2509-2520

**LCMSP 63097**

**Microsporidia species, Molecular Detection, PCR**

**Clinical Information:** Microsporidia are highly specialized fungi that cause a wide variety of clinical
syndromes in humans. The most common microsporidia are Enterocytozoon bieneusi and
Encephalitozoon intestinalis, which infect the gastrointestinal tract and cause a diarrheal illness, and
Encephalitozoon cuniculi and Encephalitozoon hellem that can infect the conjunctiva, respiratory tract,
and genitourinary system. Human infections have been reported most frequently in patients with AIDS,
but also can occur in other immunocompromised patients, including solid organ allograft recipients and,
sporadically, immunocompetent hosts. Less commonly, other microsporidia such as Vittaforma corneae
and Brachiola species can cause disseminated or organ-specific disease. This assay detects only the most
common microsporidia, Enterocytozoon bieneusi and Encephalitozoon species, and not microsporidiosis
due to other species. See Parasitic Investigation of Stool Specimens Algorithm and Laboratory Testing for
Infectious Causes of Diarrhea in Special Instructions for other diagnostic tests that may be of value in
evaluating patients with diarrhea.

**Useful For:** Detection of Enterocytozoon bieneusi and Encephalitozoon species in stool and urine
specimens to support the clinical diagnosis of microsporidiosis

**Interpretation:** A positive result indicates the presence of Enterocytozoon bieneusi and
Encephalitozoon species DNA and is consistent with an active or recent infection. Since microsporidia
dNA may be present in stool or urine in the absence of clinical symptoms, results should be correlated
with clinical presentation. A negative result indicates absence of detectable DNA from Enterocytozoon
bieneusi and Encephalitozoon species in the specimen, but does not always rule out ongoing microsporidiosis since the organism may be present at very low levels or may be sporadic. Other tests to consider in the evaluation of a patient presenting with acute or chronic watery diarrhea include cultures or specific assays for bacterial, viral, and parasitic pathogens.

Reference Values:
Negative


Microsporidia Stain

Clinical Information: Microsporidia are highly specialized fungi that cause a wide variety of clinical syndromes in humans. The most common microsporidia are Enterocytozoon bieneusi and Encephalitozoon intestinalis, which infect the gastrointestinal tract and cause a diarrheal illness, and Encephalitozoon cuniculi and Encephalitozoon hellem, which can infect the conjunctiva, respiratory tract, and genitourinary system. Human infections have been reported most frequently in patients with AIDS, but also can occur in other immunocompromised patients, including solid organ allograft recipients and, sporadically, immunocompetent hosts. Less commonly, other microsporidia such as Vittaforma corneae and Brachiola species can cause disseminated or organ-specific disease. Diagnosis of microsporidiosis is traditionally performed by light microscopic examination of stool, urine, and other specimens using a strong trichrome (chromotrope 2R) stain for detection of the characteristic spores. Unfortunately microscopic identification can be challenging due to the small size of the spores (1-4 micrometer) and their resemblance to yeast. Molecular detection using species-specific PCR offers improved sensitivity and specificity and is available for the microsporidia that cause the majority of intestinal and renal infections (ie, Encephalitozoon species and Enterocytozoon bieneusi). The microsporidia stain is reserved for use with other (non-stool and non-urine) specimen sources due to the variety of other species that may be detected outside of the intestinal tract and kidney. The antihelmintic drug, albendazole has been found effective in some infections due to Enterocytozoon bieneusi and Encephalitozoon (Septata) intestinalis.

Useful For: Diagnosis of extra-intestinal microsporidiosis involving the lung, skin, and other organs, particularly in immunocompromised hosts Diagnosis of ocular microsporidiosis

Interpretation: A positive result suggests an active or recent infection. Results should be correlated with the patient’s clinical presentation and immune status. A negative result indicates absence of detectable microsporidial spores in the specimen, but does not always rule out ongoing microsporidiosis since the organism may be present at very low levels or shed sporadically.

Reference Values:
Negative
If positive, reported as Microsporidia detected

**Midazolam (Versed), serum**

**Reference Values:**
Reference Range: 50 - 600 ng/mL

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**Milk Cow IgG4**

**Interpretation:** mcg/mL of IgG4 Lower Limit of Quantitation 0.15 Upper Limit of Quantitation 30.0

**Reference Values:**
<0.15 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicated immunologic sensitization to the food allergen in question.

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**Milk, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

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Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Milk, Processed, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE (kU/L)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;0.10</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Low Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Moderate Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>High Positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Very High</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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Mint (Mentha Piperita) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 - 0.34 Equivocal 1 0.35 - 0.69 Low Positive 2 0.70 - 3.49 Moderate Positive 3 3.50 - 17.49 High Positive 4 17.50 - 49.99 Very High
Positive 5 50.00 - 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**
<0.35 kU/L

**FMIRT 57749**
Mirtazapine (Remeron)

**Reference Values:**
Reference range: 4.0 â€“ 40.0 ng/mL

Expected steady state trough mirtazapine concentrations in patients receiving recommended daily dosages: 4.0 â€“ 40.0 ng/mL

Toxic range not established.

**ZW69 90508**
Misc Viracor Eurofins Clinical Diag

**Reference Values:**
Test Performed by: Viracor Eurofins Clinical Diag
1001 NW Technology Dr
Lee's Summit, MO 64086

**ZW199 91796**
Misc Alfred I duPont Hospital for Children

**Reference Values:**
Test Performed By: Alfred I. duPont Hospital for Children
Molecular Diagnostics Laboratory
1600 Rockland Road
Wilmington, DE 19803

**ZW200 91797**
Misc All Childrens Hospital - Florida

**Reference Values:**
Test Performed By: All Childrens Hospital - Florida
Dept of Pathology and Laboratory Medicine
801 6th Street South
St. Petersburg, Florida 33701

**ZW152 91208**
Misc Baylor Cytogenetics Laboratory

**Reference Values:**
Test performed by: Baylor Cytogenetics Laboratory
2450 Holcombe Blvd
Houston TX 770212024

**ZW201 91798**
Misc Baylor John Welsh Cardiovascular Diag Lab

**Reference Values:**
Test Performed By: Baylor College of Medicine John Walsh
Cardiovascular Diagnostics Laboratory
Dept of Pediatric Cardiology
1102 Bates, FC.480.02
Misc Cincinnati Childrens Hospital Medical Center
Reference Values:
Test Performed By: Cincinnati Childrens Hospital Medical Ctr Molecular Genetics Lab 3333 Burnet Ave Cincinnati, OH 45229

Misc Medical Neurogenetics, LLC
Reference Values:
Test Performed By: Medical Neurogenetics Lab 5424 Glenridge Drive NE Atlanta, GA 30342

Misc Monogram Biosciences, Inc.
Reference Values:
TEST PERFORMED BY: MONOGRAM BIOSCIENCES, INC. 345 OYSTER POINT BOULEVARD SOUTH SAN FRANCISCO, CA 94080

Misc National Jewish Health Mycobacteriology Test
Reference Values:
Test Performed by: National Jewish Health Mycobacteriology Lab Advanced Diagnostic Laboratories 1400 Jackson Street Denver, CO 80206-2761

Misc University of Michigan (MLabs)
Reference Values:
Test Performed by: University of Michigan (MLabs) 2900 Huron Parkway Ann Arbor, MI 48105

Miscellaneous Alfred I duPont Gastroenterology
Reference Values:
Test Performed By: Alfred I. duPont Hospital for Children Nemours Children's Clinic Division of Gastroenterology/Nutrition Gastroenterology Laboratory 1600 Rockland Rd.-Research Bldg. Rm 250 Wilmington, DE 19803
**Miscellaneous BloodCenter of WI Testing**

Reference Values:
Test Performed by: BloodCenter of Wisconsin  
638 N. 18th Street  
Milwaukee, WI 53233

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**Miscellaneous Cambridge Biomedical**

Reference Values:
Test Performed by: Cambridge Biomedical Inc.  
1320 Soldiers Field Road  
Boston, MA 02135

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**Miscellaneous Center for Genetic Testing at St. Francis**

Reference Values:
Test Performed by: Center for Genetic Testing  
St. Francis Hosp-Genetics Lab  
6161 S. Yale Ave.  
Tulsa, OK 74136

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**Miscellaneous Chemistry Testing**

Reference Values:  
Varies

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**Miscellaneous Child Hosp-Philadelphia**

Reference Values:  
Test Performed by: The Children’s Hospital of Philadelphia  
Main Bldg 5th Floor Rm 5NWS55  
34th Street and Civic Center Blvd  
Philadelphia, PA 19104

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**Miscellaneous Childrens Hospital of Colorado Testing**

Reference Values:  
Test Performed by: Childrens Hospital of Colorado  
13123 E 16th Ave  
Aurora, CO 80045

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**Miscellaneous Chlamydia trachomatis and Neisseria gonorrhoeae by Nucleic Acid Amplification**

Clinical Information: Chlamydia is caused by the obligate intracellular bacterium Chlamydia trachomatis and is the most prevalent sexually transmitted bacterial infection in the United States.(1,2) In 2010, 1.3 million documented cases were reported to the CDC.(2) Given that 3 out of 4 infected women and 1 out of 2 infected men will be asymptomatic initially, the actual prevalence of disease is thought to be much greater than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria and vaginal, urethral, or rectal discharge. In women,
Complications include pelvic inflammatory disease, salpingitis, and infertility. Approximately 25% to 30% of women who develop acute salpingitis become infertile. (2) Complications among men are rare, but include epididymitis and sterility. Rarely, genital chlamydial infection can cause arthritis with associated skin lesions and ocular inflammation (Reiter syndrome). C trachomatis can be transmitted from the mother during delivery and is associated with conjunctivitis and pneumonia. Finally, C trachomatis may cause hepatitis and pharyngitis in adults. Once detected, the infection is easily treated by a short course of antibiotic therapy. Annual chlamydia screening is now recommended for all sexually active women age 25 years and younger, and for older women with risk factors for infection, such as a new sex partner or multiple sex partners. The CDC also recommends that all pregnant women be given a screening test for Chlamydia infection. (2) Repeat testing for test-of-cure is not recommended after treatment with a standard treatment regimen unless patient compliance is in question, reinfection is suspected, or the patient’s symptoms persist. Repeat testing of pregnant women, 3 weeks after completion of therapy, is also recommended to ensure therapeutic cure. (2) Gonorrhea is caused by the bacterium Neisseria gonorrhoeae. It is also a very common sexually transmitted infection (STI), with 301,174 cases of gonorrhea reported to CDC in 2009. (2, 3) Many infections in women are asymptomatic and the true prevalence of gonorrhea is likely much higher than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria and vaginal, urethral, or rectal discharge. Complications include pelvic inflammatory disease in women and gonococcal epididymitis and prostatitis in men. Gonococcal bacteremia, pharyngitis, and arthritis may also occur. Infection in men is typically associated with symptoms that would prompt clinical evaluation. Given the risk for asymptomatic infection in women, screening is recommended for women at increased risk of infection (eg, women with previous gonorrhea or other STI, inconsistent condom use, new or multiple sex partners, and women in certain demographic groups such as those in communities with high STI prevalence). (2, 3) The CDC currently recommends dual antibiotic treatment due to emerging antimicrobial resistance. (2) Culture was previously considered to be the gold standard test for diagnosis of C trachomatis and N gonorrhoeae infections. (2) However, organisms are labile in vitro, and precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now the recommended method for diagnosis in most cases. (4-6) Immunoassays and nonamplification DNA tests are also available for C trachomatis and N gonorrhoeae detection, but these methods are significantly less sensitive and less specific than NAAT. (2) Improved screening rates and increased sensitivity of NAAT testing have resulted in an increased number of accurately diagnosed cases of both chlamydia and gonorrhea. (2-6) Improved detection rates result from both the increased performance of the assay and the patients’ easy acceptance of urine testing. Early identification of infection enables sexual partners to seek testing and/or treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

Useful For: Detection of Chlamydia trachomatis and Neisseria gonorrhoeae in non-FDA-approved specimen types

Interpretation: A positive result indicates that rRNA of Chlamydia trachomatis and/or Neisseria gonorrhoeae is present in the specimen tested and strongly supports a diagnosis of chlamydial/gonorrheal infection. A negative result indicates that rRNA for C trachomatis and/or N gonorrhoeae was not detected in the specimen. The predictive value of an assay depends on the prevalence of the disease in any particular population. In settings with a high prevalence of sexually transmitted disease, positive assay results have a high likelihood of being true positives. In settings with a low prevalence of sexually transmitted disease, or in any setting in which a patient’s clinical signs and symptoms or risk factors are inconsistent with gonococcal or chlamydial urogenital infection, positive results should be carefully assessed and the patient retested by other methods (eg, culture for N gonorrhoeae), if appropriate. A negative result does not exclude the possibility of infection. If clinical indications strongly suggest gonococcal or chlamydial infection, additional specimens should be collected for testing. A result of indeterminate indicates that a new specimen should be collected. This test has not been shown to cross react with commensal (nonpathogenic) Neisseria species present in the oropharynx.

Reference Values:

Negative

Clinical References: 1. Centers for Disease Control and Prevention. 2014. Recommendations for the...

ZW279 Miscellaneous Cincinnati Children's Nephrology
Reference Values:
Test Performed by: Cincinnati Children’s Nephrology
3333 Burnet Avenue
Cincinnati, OH 45229

ZW193 Miscellaneous Connective Tissue Gene Tests Lab (CTGT)
Reference Values:
Test Performed By: Connective Tissue Gene Tests, LLC
6575 Snowdrift Road, Suite 106
Allentown, PA 18106

ZW212 Miscellaneous Correlagen Diagnostics
Reference Values:
Test Performed By: Correlagen Diagnostics
3400 Computer Drive, Suite 100
Westborough, MA 01581

ZW130 Miscellaneous DIANON Systems
Reference Values:
Varies
Test Performed by: DIANON Systems, Inc.
1 Forest Parkway
Shelton, CT 06484

ZW57 Miscellaneous Esoterix Coagulation
Reference Values:
Varies
Test Performed by: Esoterix Coagulation
8490 Upland Dr
Suite 100
ZW189  Miscellaneous Esoterix Genetic Laboratories, LLC - NY Testing
Reference Values:
Test Performed by: Esoterix Genetic NY
521 West 57th Street
6th Floor
New York, NY 10019

ZW208  Miscellaneous Genetic Assays Inc.
Reference Values:
Test Performed By: Genetic Assays, Inc.
4711 Trousdale Drive
Suite 209
Nashville, TN 37220

ZW182  Miscellaneous Genova Diagnostics
Reference Values:
Test Performed by: Genova Diagnostics
63 Zillicoa Street
Asheville, NC 28801-1074

ZW218  Miscellaneous Harvard Medical School
Reference Values:
Test Performed by: Harvard Medical School and Partners Healthcare Laboratory for Molecular Medicine,
Center for Genetics and Genomics
65 Landsdowne Street
Cambridge, MA 02139

ZW134  Miscellaneous INFORM DIAGNOSTICS, INC
Reference Values:
Test Performed by: INFORM DIAGNOSTICS, INC
4207 E Cotton Center Blvd
Phoenix, AZ 85040-8893

ZW173  Miscellaneous Joli Diagnsotics, Inc.
Reference Values:
Test Performed by: Joli Diagnostic
2451 Wehrle Drive
Williamsville, NY 14221

ZW241  Miscellaneous Knight Diagnostic Laboratories
Reference Values:
Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Reference Values:
Test Performed by: Knight Diagnostic Laboratories
2525 S.W. 3rd Ave.
Portland, OR 97201-3098

**ZW266**
**58067**

**Miscellaneous Machaon Diagnostics**
Reference Values:
Test Performed by: Machaon Diagnostics, Inc.
3023 Summit St.
Oakland, CA 94609

**ZW207**
**91852**

**Miscellaneous MD Anderson Cancer Center**
Reference Values:
Test Performed By: MD Anderson Cancer Center
Division of Laboratory Medicine
1515 Holcombe Boulevard
Houston, TX 77030

**ZW79**
**90518**

**Miscellaneous Med Coll of WI**
Reference Values:
Test Performed by: Medical College of WI
MACC Fund Research Center, Room 5035
Dr. Nita Salzman, M.D., Ph.D.
8701 Watertown Plank Road
Milwaukee, WI 53226

**ZW78**
**90517**

**Miscellaneous Medical Coll of WI**
Reference Values:
Test Performed by: Medical College of WI
MACC Fund Research Center, Room 5068
Jordan N. Fink, M.D.
Allergy-Immunology Diagnostic Lab
8701 Watertown Plank Road
Milwaukee, WI 53226

**ZW2**
**99992**

**Miscellaneous MML Referral Test 2**
Clinical Information: NA
Reference Values:
Varies with test

**ZW3**
**99993**

**Miscellaneous MML Referral Test 3**
Reference Values:
Vary with test requested.
Miscellaneous National Jewish Health

Reference Values:
Test Performed by: National Jewish Health
Advanced Diagnostic Laboratories
1400 Jackson Street
Denver, CO 80206-2761

Miscellaneous Ohio State Univ Molecular Pathology

Reference Values:
Test Performed By: Ohio State University Molecular Pathology Laboratory
173 Hamilton Hall
1645 Neil Avenue
Columbus, OH 43210

Miscellaneous OneOme, LLC

Reference Values:
Test Performed by: OneOme, LLC
807 Broadway Street NE Suite 100
Minneapolis, MN 55413

Miscellaneous Oregon Health and Science University Ocular Immunology Laboratory

Reference Values:
Test Performed By: Oregon Health and Science University Ocular Immunology Laboratory
Casey Eye Institute, BRB Room 253
3181 SW Sam Jackson Road
Portland, OR 97239

Miscellaneous Pacific Rim Pathology Medical Corp

Reference Values:
Test Performed by: Pacific Rim Pathology Medical Corp.
5325 Metro St. STE A
San Diego, CA 92110-2608

Miscellaneous Prevention Genetics Lab

Reference Values:
Test Performed By: Prevention Genetics Lab Diagnostics Lab
3700 Downwind Drive
Marshfield, WI 54449

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 1508
**MISCF 35267**

**Miscellaneous Studies Using Chromosome-Specific Probes, FISH**

**Clinical Information:** Conventional cytogenetic studies can identify the presence of chromosome abnormalities and most mosaic conditions. In approximately 2% of these chromosomally abnormal cases, the genetic makeup of the chromosome abnormality can be identified, but not completely characterized, by conventional techniques alone. For malignant disorders, the proportion of specimens with unresolvable chromosome abnormalities is much higher. Chromosomal microarray analysis (CMA) can detect copy number gain or loss of a chromosomal region but cannot identify the mechanism. FISH using gene-specific probes and various probe strategies can help characterize chromosome abnormalities. This includes abnormalities that cannot be accurately characterized by chromosome analysis or CMA such as unusual structural alterations, and unbalanced chromosome abnormalities such as deletions, duplications, and translocations. Scoring large numbers of interphase nuclei can more accurately establish the frequency of chromosome abnormalities and assess level of mosaicism.

**Useful For:** Resolution of unusual or complex structural alterations, questionable mosaicism, and unbalanced chromosome abnormalities that cannot be resolved by chromosome or chromosomal microarray analysis. Identifying gain, loss, or rearrangement of chromosome regions using gene or locus-specific probes.

**Interpretation:** An interpretive report is provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
ZW288 75170  
**Miscellaneous UF Health Medical Lab-Shands Hospital**  
**Reference Values:**  
Test Performed by:  
UF Health Medical Lab-Shands Hospital  
Infectious Disease Pharmacokinetics Laboratory  
1600 SW Archer Rd., P4-30  
Gainesville, FL 32610  

ZW292 75215  
**Miscellaneous UNC Center for AIDS Research Clinical Pharmacology & Analytical Chemistry Laboratory**  
**Reference Values:**  
Test Performed by:  
UNC CFAR Clinical Pharmacology and Analytical Chemistry Lab  
120 Mason Farm Road, CB# 7361  
1100 Genetic Medicine Building  
Chapel Hill, NC 27599  

ZW99 90538  
**Miscellaneous Univ of AL Testing**  
**Reference Values:**  
Test Performed by: University of Alabama-Birmingham  
648 Kaul Building  
720 20th Street South  
Birmingham, AL 35233  

ZW210 91857  
**Miscellaneous Univ of IA Molecular Otolaryngology**  
**Reference Values:**  
Test Performed By: Univ of IA Molecular Otolaryngology  
Research Laboratory  
5270 Carver Biomedical Research Building  
Iowa City, IA 52242  

ZW186 91515  
**Miscellaneous University of Chicago Genetics Services**  
**Reference Values:**  
Test Performed by: University of Chicago Genetics Services  
5841 S. Maryland Ave.  
Room 035, M/C 0077  
Chicago, IL 60637  

ZW187 91514  
**Miscellaneous University of Iowa Diagnostic Labs**  
**Reference Values:**  
Test Performed by: UI Diagnostic Laboratories  
Department of Pathology  
200 Hawkins Drive, Rm 5231 RCP  
Iowa City, IA 52242
Miscellaneous University of Minnesota Outreach Laboratory

Reference Values:
Test Performed by: Univ of MN Outreach Laboratories
420 Delaware St. S.E.
Minneapolis, MN 55455

Miscellaneous University of Texas Health Center at Tyler Microbiology

Reference Values:
Test Performed By: University of Texas Health Center
Department of Microbiology
11937 US Hwy 271
Tyler, TX 75708

Miscellaneous University of Utah Genome Center

Reference Values:
Test Performed By: University of Utah Genome Center
20 South 2030 East
Biomedical Polymers Building 570
Room 308
Salt Lake City, UT 84112-9454

Miscellaneous University of Washington Medical Center (UW Virology Dept of Lab Medicine)

Reference Values:
Test Performed by: UW Virology Dept of Lab Medicine,
1616 Eastlake Ave E
Ste 320 BOX 358115
Seattle, WA 98102

Miscellaneous University of Washington Medical Center-Clinical Immunology Lab

Reference Values:
Test Performed by: University of Washington Medical Center-Clinical Immunology Lab
1959 NE Pacific St. Room NW220
Seattle, WA 98195-0001

Miscellaneous UPMC Molecular and Genomic Pathology

Reference Values:
Test Performed by: UPMC Molecular and Genomic Pathology
3477 Euler Way
Pittsburgh, PA 15213
Mismatch Repair (MMR) Protein Immunohistochemistry Only, Tumor

Clinical Information: Hereditary nonpolyposis colon cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant inherited cancer syndrome that predisposes individuals to the development of colorectal, endometrial, gastric, upper urinary tract, and other cancers. Individuals with HNPCC/Lynch syndrome have a germline mutation in 1 of several genes involved in DNA mismatch repair. The majority of mutations associated with HNPCC/Lynch syndrome occur in MSH2 and MLH1; however mutations in MSH6 and PMS2 have also been identified. There are several strategies for evaluating individuals whose personal and/or family history of cancer is suggestive of HNPCC/Lynch syndrome. Typically, the first step is to evaluate tumors for the characteristics common to individuals with HNPCC/Lynch syndrome which include microsatellite instability (presence of numerous alterations in a type of repetitive DNA called microsatellites) and loss of protein expression of 1 or more of the genes associated with HNPCC/Lynch syndrome. Microsatellite instability (MSI) and immunohistochemistry (IHC) are commonly interpreted together to evaluate risk for HNPCC/Lynch syndrome. High levels of MSI within a tumor are suggestive of defective DNA mismatch repair, however this finding does not provide information about which gene is involved. IHC is a complementary testing strategy used to evaluate the expression of the MLH1, MSH2, MSH6, and PMS2 proteins in HNPCC/Lynch syndrome related cancers. Loss of expression of 1 or more of these proteins within the tumor is helpful in identifying which corresponding gene(s) to target for mutation analysis. Although MSI and IHC are best interpreted together, they are also available separately to accommodate clinical situations in which there are barriers to performing these tests concurrently (e.g., financial concerns, specimen requirements). IHC alone can determine retention or loss of MLH1, MSH2, MSH6, and PMS2 protein expression. If all 4 proteins are present, the likelihood of HNPCC/Lynch syndrome is reduced but not eliminated because approximately 5% of tumors that display MSI also have normal protein expression for these 4 genes. Loss of 1 or more proteins by IHC is suggestive of defective DNA mismatch repair within the tumor and the likelihood of HNPCC/Lynch syndrome is increased. Germine testing (ie, mutation analysis) for the corresponding gene(s) can then be performed to identify the causative germline mutation and allow for predictive testing of at risk individuals. Of note, loss of protein expression by IHC has also been demonstrated in various sporadic cancers, including those of the colon and endometrium. Absence of MLH1 and PMS2 protein expression within a tumor, for instance, is most often associated with a somatic alteration in individuals with an older age of onset of cancer than typical HNPCC/Lynch syndrome families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between somatic and germline mutations. Genetic testing of the gene indicated by IHC analysis can help to distinguish between these 2 possibilities. In addition, when absence of MLH1/PMS2 are observed, BRMLH / MLH1 Hypermethylation and BRAF Mutation Analyses, Tumor or ML1HM / MLH1 Hypermethylation Analysis, Tumor may also help to distinguish between a sporadic and germline etiology. It should be noted that this is not a genetic test, but rather stratifies the risk of having an inherited cancer predisposition syndrome, and identifies patients who might benefit from subsequent genetic testing. See Lynch Syndrome Testing Algorithm in Special Instructions for additional information.

Useful For: Evaluation of tumor tissue to identify patients at risk for having hereditary nonpolyposis colon cancer/Lynch syndrome Note: Mayo's preferred screening test, MSIHC / Microsatellite Instability (MSI)/Immunohistochemistry (IHC) Profile-Lynch/Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Screen, includes both microsatellite instability and immunohistochemistry testing.

Interpretation: An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.

**MITF Immunostain, Technical Component Only**

**Clinical Information:** Microphthalmia-associated transcription factor (MiTF) is produced by melanocytes and osteoclasts and can be useful in the classification of melanoma.

**Useful For:** Identification of melanomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Mitochondrial Antibodies (M2), Serum**

**Clinical Information:** Antimitochondrial antibodies (AMAs) are detectable by indirect immunofluorescence in >90% of patients with primary biliary cirrhosis (PBC), but this method also detects AMAs of differing specificities in other diseases. The mitochondrial antigens recognized by AMAs in patients' sera have been classified numerically as M1 through M9, with the M2 antigen complex recognized by AMAs in sera from patients with PBC. M2 antigen is comprised of enzyme proteins of the 2-oxoacid dehydrogenase complex that are located on inner mitochondrial membranes. Included in this group of autoantigens are the pyruvate dehydrogenase complex, and 2-oxoglutarate dehydrogenase complex.

**Useful For:** Establishing the diagnosis of primary biliary cirrhosis

**Interpretation:** Positive results for antimitochondrial antibody (AMA) of M2 specificity are highly specific for primary biliary cirrhosis (PBC), and false-negative results are rare. A positive result for AMA of M2 specificity in a patient with clinical features of PBC is virtually diagnostic for this disease.

**Reference Values:**
- Negative: <0.1 Units
- Borderline: 0.1-0.3 Units
- Weakly positive: 0.4-0.9 Units
- Positive: > or =1.0 Units

Reference values apply to all ages.

**Clinical References:**
Mitochondrial Full Genome Analysis by Next-Generation Sequencing (NGS)

Clinical Information: The mitochondrion occupies a unique position in eukaryotic biology. First, it is the site of energy metabolism, without which aerobic metabolism and life as we know it would not be possible. Second, it is the sole subcellular organelle that is composed of proteins derived from 2 genomes, mitochondrial and nuclear. A group of hereditary disorders due to mutations in either the mitochondrial genome or nuclear mitochondrial genes have been well characterized. The diagnosis of mitochondrial disease can be particularly challenging as the presentation can occur at any age, involving virtually any organ system, and with widely varying severities. This test utilizes massively parallel sequencing, also termed next-generation sequencing (NGS) to determine the exact sequence of the entire 16,569 base-pair mitochondrial genome. The utility of this test is to assist in the diagnosis of the subset of mitochondrial diseases that result from mutations in the mitochondrial genome (mtDNA). This includes certain types of myopathies and neuro-ophthalmologic diseases, such as mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibers (MERRF), mitochondrial myopathy (MM), neurogenic muscle weakness, ataxia, retinitis pigmentosa (NARP), Leigh syndrome, Leber hereditary optic neuropathy (LHON), and chronic progressive external ophthalmoplegia (CPEO). In addition to the detection of single base changes with these disorders, large deletions, such as those associated with Kearns-Sayre or Pearson syndromes, are also detected. Mutations in mitochondrial proteins that are encoded by genes in the nucleus, such as the enzymes of fatty acid oxidation, are not detected using this test. In contrast to mutations in nuclear genes, which are present in either 0, 1, or 2 copies, mitochondrial mutations can be present in any fraction of the total organelles, a phenomenon known as heteroplasmy. Typically, the severity of disease presentation is a function of the degree of heteroplasmy. Individuals with a higher fraction of mutant mitochondria present with more severe disease than those with lower percentages of mutant alleles. The sensitivity for the detection of mutant alleles in a background of wild-type (or normal) mitochondrial sequences by NGS is approximately 10%.

Useful For: Diagnosis of the subset of mitochondrial diseases that results from mutations in the mitochondrial genome A second-tier test for patients in whom previous targeted gene mutation analyses for specific mitochondrial disease-related genes were negative Identifying mutations within genes of the mitochondrial genome that are known to be associated with mitochondrial disease, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. The degree of heteroplasmy of each single nucleotide or INDEL variant, defined as the ratio (percentage) of variant sequence reads to the total number of reads, will also be reported. Large deletions will be reported as either homoplasmic or heteroplasmic, but the degree of heteroplasmy will not be estimated, due to possible preferential amplification of the smaller deletion product by long-range PCR.

Reference Values: An interpretive report will be provided.

Sequencing (NGS)

Clinical Information: The mitochondrion occupies a unique position in eukaryotic biology. It is the site of energy metabolism, and it is the sole subcellular organelle that is composed of proteins derived from 2 genomes, mitochondrial and nuclear. A group of hereditary disorders due to mutations in either the mitochondrial genome or nuclear mitochondrial genes has been well characterized. The diagnosis of mitochondrial disease can be particularly challenging as the presentation can occur at any age, involve virtually any organ system, and be associated with widely varying severities. Due to the considerable overlap in the clinical phenotypes of various mitochondrial disorders, it is often difficult to distinguish these specific inherited disorders without genetic testing. This test utilizes massively parallel sequencing, also termed next-generation sequencing (NGS), to analyze 176 nuclear-encoded genes implicated in mitochondrial disease. The utility of this test is to assist in the diagnosis of the subset of mitochondrial diseases that result from mutations in the nuclear encoded genes. This includes disorders of mitochondrial protein synthesis, disorders of coenzyme Q10 biosynthesis, disorders of the respiratory chain complexes and disorders of mtDNA maintenance (ie, mitochondrial DNA depletion disorders). See Targeted Genes Interrogated by Mitochondrial Nuclear Gene Panel in Special Instructions for details regarding the targeted genes identified by this test.

Useful For: Diagnosis of the subset of mitochondrial disease that results from mutations in the nuclear-encoded genes A second-tier test for patients in whom previous targeted gene mutation analyses for specific mitochondrial disease-related genes were negative Identifying mutations within genes of the nuclear genome that are known to be associated with mitochondrial disease, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.


Mitochondrial Respiratory Chain Enzyme Analysis (ETC) - Skin Fibroblasts

Reference Values:
A final report will be attached in Mayo Access.


**Mitotane (Lysodren)**

**Reference Values:**

Units: ug/mL

Therapeutic and toxic ranges have not been established.

Usual therapeutic doses produce Mitotane serum concentrations of less than 100 ug/mL.

**MLH-1, Immunostain (Bill Only)**

**Reference Values:**

This test is for billing purposes only.

This is not an orderable test.

**MLH1 Gene, Full Gene Analysis**

**Clinical Information:** Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC) is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3-prime end of the EPCAM gene have also been associated with Lynch syndrome, as this leads to inactivation of the MSH2 promoter. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer-associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome-related genes. The lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are <15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described, but also include brain/central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of Lynch syndrome. One such strategy involves testing the tumors from suspected individuals for microsatellite instability (MSI) and immunohistochemistry (IHC) for the presence or absence of defective DNA mismatch repair. Tumors that demonstrate absence of expression of MLH1 and PMS2 are more likely to have a germline mutation in the MLH1 gene.

**Useful For:** Determining whether absence of MLH1 protein, by immunohistochemistry in tumor tissue, is associated with a germline mutation in the affected individual. Establishing a diagnosis of Lynch syndrome/hereditary nonpolyposis colorectal cancer. Identification of familial MLH1 mutation to allow for predictive testing in family members.

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.
**Reference Values:**
An interpretive report will be provided.


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**BMLHH**

**MLH1 Hypermethylation Analysis (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

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**MLHPB**

**MLH1 Hypermethylation Analysis, Blood**

**Clinical Information:** Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC) is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3-prime end of the EPCAM gene have also been associated with Lynch syndrome/HNPCC, as this leads to inactivation of the MSH2 promoter. Lynch syndrome/HNPCC is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome/HNPCC-related genes and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are <15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome/HNPCC spectrum. Several clinical variants of Lynch syndrome/HNPCC have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described, but also include brain and central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of Lynch syndrome/HNPCC. One such strategy involves testing the tumors from suspected individuals for microsatellite instability (MSI) and/or immunohistochemistry (IHC) for the presence or absence of defective DNA mismatch repair. It is important to note, however, that the MSI-H tumor phenotype is not restricted to inherited cancer cases; approximately 20% of sporadic colon cancers are MSI-H. Thus, MSI-H does not distinguish between a somatic (sporadic) and a germline (inherited) mutation, nor does it identify which gene is involved. Although IHC analysis is helpful in identifying the responsible gene, it also does not distinguish between somatic and germline defects. Defective mismatch repair in sporadic colon cancer is most often due to an abnormality in MLH1, and the most common cause of gene inactivation is promoter hypermethylation (epigenetic silencing). A specific mutation in the BRAF gene (V600E) has been shown to be present in approximately 70% of tumors with hypermethylation of the MLH1 promoter. Importantly, the V600E mutation is rarely identified in cases with germline MLH1 mutations. Thus, direct assessment of MLH1 promoter methylation status and testing for the BRAF V600E
mutation can be used to help distinguish between a germline mutation and epigenetic/somatic inactivation of MLH1. Tumors that have the BRAF V600E mutation and demonstrate MLH1 promoter hypermethylation are almost certainly sporadic, whereas tumors that show neither are most often caused by an inherited mutation. However, individuals with tumor hypermethylation may additionally have MLH1 promoter hypermethylation consistent with germline inactivation. Individuals with germline inactivation of MLH1 by promoter hypermethylation are at an increased risk for Lynch syndrome/HNPCC-related tumors. In contrast to sequence mutations in MLH1, current evidence suggests that the risk of transmitting germline MLH1 promoter hypermethylation is <50%.

**Useful For:** As an adjunct to positive hypermethylation in tumor to distinguish between somatic and germline hypermethylation
As an adjunct to negative MLH1 germline testing in cases where colon or endometrial tumor demonstrates microsatellite instability-H (MSI-H) and loss of MLH1 protein expression

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Interpretive report will be provided.

**Clinical References:**

**ML1HM**

**MLH1 Hypermethylation Analysis, Tumor**

**Clinical Information:** Hereditary nonpolyposis colon cancer (HNPCC), also known as Lynch syndrome, is an inherited cancer syndrome caused by a germline mutation in one of several genes involved in DNA mismatch repair (MMR), including MLH1, MSH2, MSH6 and PMS2. There are several laboratory-based strategies that help establish the diagnosis of HNPCC/Lynch syndrome, including testing tumor tissue for the presence of microsatellite instability (MSI-H) and loss of protein expression for any one of the MMR proteins by immunohistochemistry (IHC). It is important to note, however, that the MSI-H tumor phenotype is not restricted to inherited cancer cases; approximately 20% of sporadic colon cancers are MSI-H. Thus, MSI-H does not distinguish between a somatic (sporadic) and a germline (inherited) mutation, nor does it identify which gene is involved. Although IHC analysis is helpful in identifying the responsible gene, it also does not distinguish between somatic and germline defects. Defective MMR in sporadic colon cancer is most often due to an abnormality in MLH1, and the most common cause of gene inactivation is promoter hypermethylation (epigenetic silencing). A specific mutation in the BRAF gene (V600E) has been shown to be present in approximately 70% of tumors with hypermethylation of the MLH1 promoter. Importantly, the V600E mutation is rarely identified in cases with germline MLH1 mutations. Thus, direct assessment of MLH1 promoter methylation status and testing for the BRAF V600E mutation can be used to help distinguish between a germline mutation and epigenetic/somatic inactivation of MLH1. Tumors that have the BRAF V600E mutation and demonstrate MLH1 promoter hypermethylation are almost certainly sporadic, whereas tumors that show neither are most often caused by an inherited mutation. Although testing for the BRAF V600E mutation and MLH1 promoter hypermethylation are best interpreted together, they are also available separately to accommodate various clinical situations and tumor types. These tests can provide helpful diagnostic information when evaluating an individual suspected of having HNPCC/Lynch syndrome, especially when testing is performed in conjunction with MSHC / Microsatellite Instability (MSI)/Immunohistochemistry (IHC) Profile-Lynch/Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Screen, which includes MSI and IHC studies. It should be noted that these tests are not genetic tests, but rather stratify the risk of having an inherited cancer predisposition and identify patients who might benefit from subsequent genetic testing. See Lynch Syndrome Testing Algorithm in Special Instructions.
**Useful For:** An adjunct to MSIHC / Microsatellite Instability (MSI)/Immunohistochemistry (IHC) Profile-Lynch/Hereditary Nonpolyposis Colorectal Cancer (HNPPC) Screen, when colon or endometrial tumor demonstrates microsatellite instability (MSI-H) and loss of MLH1 protein expression, to help distinguish a somatic versus germline event prior to performing expensive germline testing. An adjunct to negative MLH1 germline testing in cases where colon or endometrial tumor demonstrates MSI-H and loss of MLH1 protein expression. Note: Mayo's preferred screening test (BRMLH / MLH1 Hypermethylation and BRAF Mutation Analyses, Tumor) includes both MLH1 promoter hypermethylation and BRAF V600E testing. Please note that this test can only be performed on colon tumors.

**Interpretation:** An interpretive report will be provided. The likelihood of a germline (inherited) mutation is very low in those cases where the tumor demonstrates MLH1 promoter hypermethylation and the normal tissue is unmethylated. The likelihood of a germline mutation is high in those cases where the tumor and normal tissue lack MLH1 promoter hypermethylation. In cases where the tumor and normal tissue demonstrate MLH1 promoter hypermethylation, this result will be interpreted as equivocal and a blood sample will be requested to confirm potential germline hypermethylation.

**Reference Values:**
An interpretative report will be provided.

**Clinical References:**

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**BRMLH**

**MLH1 Hypermethylation and BRAF Mutation Analysis, Tumor**

**Clinical Information:** Hereditary nonpolyposis colon cancer (HNPCC), also known as Lynch syndrome, is an inherited cancer syndrome caused by a germline mutation in 1 of several genes involved in DNA mismatch repair (MMR), including MLH1, MSH2, MSH6, and PMS2. There are several laboratory-based strategies that help establish the diagnosis of HNPCC/Lynch syndrome, including testing tumor tissue for the presence of microsatellite instability (MSI-H) and loss of protein expression for any of the MMR proteins by immunohistochemistry (IHC). It is important to note, however, that the MSI-H tumor phenotype is not restricted to inherited cancer cases; approximately 20% of sporadic colon cancers are MSI-H. Thus, MSI-H does not distinguish between a somatic (sporadic) and a germline (inherited) mutation, nor does it identify which gene is involved. Although IHC analysis is helpful in identifying the responsible gene, it also does not distinguish between somatic and germline defects. Defective MMR in sporadic colon cancer is most often due to an abnormality in MLH1, and the most common cause of gene inactivation is promoter hypermethylation (epigenetic silencing). A specific mutation in the BRAF gene (V600E) has been shown to be present in approximately 70% of tumors with hypermethylation of the MLH1 promoter. Importantly, the V600E mutation is rarely identified in cases with germline MLH1 mutations. Thus, direct assessment of MLH1 promoter methylation status and testing for the BRAF V600E mutation can be used to help distinguish between a germline mutation and epigenetic/somatic inactivation of MLH1. Tumors that have the BRAF V600E mutation and demonstrate MLH1 promoter hypermethylation are almost certainly sporadic, whereas tumors that show neither are most often caused by an inherited mutation. Although testing for the BRAF V600E mutation and MLH1 promoter hypermethylation are best interpreted together, they are also available separately to accommodate various clinical situations and tumor types. These tests can provide helpful diagnostic information when evaluating an individual suspected of having HNPCC/Lynch syndrome, especially when testing is performed in conjunction with MSIHC / Microsatellite Instability (MSI)/Immunohistochemistry (IHC) Profile-Lynch/Hereditary Nonpolyposis Colorectal Cancer (HNPPC) Screen, which includes MSI and IHC studies. It should be noted that these
tests are not genetic tests, but rather stratify the risk of having an inherited cancer predisposition and identify patients who might benefit from subsequent genetic testing. See Lynch Syndrome Testing Algorithm in Special Instructions.

**Useful For:** An adjunct to MSIHC / Microsatellite Instability (MSI)/Immunohistochemistry (IHC) Profile-Lynch/Hereditary Nonpolyposis Colorectal Cancer (HNPPC) Screen, when colon tumor demonstrates microsatellite instability (MSI-H) and loss of MLH1 protein expression, to help distinguish a somatic versus germline event prior to performing expensive germline testing An adjunct to negative MLH1 germline testing in cases where colon tumor from the same patient demonstrates MSI-H and loss of MLH1 protein expression

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**MLH1 Immunostain, Technical Component Only**

**Clinical Information:** Hereditary nonpolyposis colorectal cancer (HNPPC), also known as Lynch syndrome, is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes: MLH1, MSH2, MSH6, and PMS2. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome-related genes and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include sebaceous neoplasms, gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are less than 15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described but also include brain and central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous or compound heterozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of Lynch syndrome. Testing tumors from individuals at risk for Lynch syndrome for microsatellite instability (MSI) indicates the presence or absence of defective DNA mismatch repair phenotype within the tumor, but does not suggest in which gene the abnormality rests. Tumors from individuals affected by Lynch syndrome usually demonstrate an MSI-H phenotype (MSI >30% of microsatellites examined). The MSI-H phenotype can also be seen in individuals whose tumors have somatic MLH1 promoter hypermethylation. Tumors from individuals that show the MSS/MSI-L phenotype (MSI at <30% of microsatellites examined), are not likely to have Lynch syndrome or somatic hypermethylation of MLH1. Immunohistochemistry (IHC) is a complementary testing strategy to MSI testing. In addition to identifying tumors with defective DNA mismatch repair, IHC analysis is helpful for identifying the gene responsible for the defective DNA mismatch repair within the tumor, because the majority of MSI-H
tumors show a loss of expression of at least 1 of the 4 mismatch repair genes described above. Testing is typically first performed on the tumor of an affected individual and in the context of other risk factors, such as young age at diagnosis or a strong family history of Lynch syndrome-related cancers. If defective DNA mismatch repair is identified within the tumor, mutation analysis of the associated gene can be performed to identify the causative germline mutation and allow for predictive testing of at-risk individuals. Of note, MSI-H phenotypes and loss of protein expression by IHC have also been demonstrated in various sporadic cancers, including those of the colon and endometrium. Absence of MLH1 and PMS2 protein expression within a tumor, for instance, is most often associated with a somatic alteration in individuals with an older age of onset of cancer than typical Lynch syndrome families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between somatic and germline mutations. Genetic testing of the gene indicated by IHC analysis can help to distinguish between these 2 possibilities. In addition, when absence of MLH1/PMS2 is observed, BRMLH / MLH1 Hypermethylation and BRAF Mutation Analyses, Tumor or ML1HM / MLH1 Hypermethylation Analysis, Tumor may also help to distinguish between a sporadic and germline etiology. It should be noted that this Lynch syndrome screen is not a genetic test, but rather stratifies the risk of having an inherited cancer predisposition syndrome, and identifies patients who might benefit from subsequent genetic testing.

**Useful For:** Evaluation of tumor tissue to identify patients at high risk for having hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome Evaluation of tumor tissue to identify patients at risk for having hereditary endometrial carcinoma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.


**MLH3Z**

**MLH3 Gene, Full Gene Analysis**

**Clinical Information:** MLH3 is a gene that has been investigated in regards to its role in hereditary colorectal cancer. Current literature suggests that alterations in the MLH3 gene are found more often in the disease population than in healthy controls. Therefore, individuals with a mutation in MLH3 may be at an increased risk for colorectal cancer. However, mutations in MLH3 have been seen in both family
members with disease and healthy relatives, indicating reduced penetrance. Also, it has been suggested that MLH3 is a low-risk gene for colorectal cancer. When mutations in MLH3 are seen with mutations in other genes associated with colorectal cancer, the genes may work in an additive manner, further elevating risk. In addition to patients with colorectal cancer, MLH3 alterations have been reported in individuals with endometrial and esophageal cancers. Current literature suggests that in some families MLH3 may act as a low-risk gene for esophageal cancer. Additionally, MLH3 may play a role in endometrial tumorigenesis, with involvement in initiation and/or progression of endometrial cancers. There is conflicting evidence in the literature regarding the ability of mutations in MLH3 to alter mismatch repair (MMR). Some studies suggest that MLH3 mutations can affect DNA mismatch repair, resulting in microsatellite instability (MSI), while others say mutations in MLH3 alone do not interfere with MMR. Alterations have been reported in both microsatellite stable (MSS)/MSI-low tumors and MSI-high tumors. However, some of these MSI-H tumors also had loss reported with immunohistochemistry. Additional research is needed to fully understand the relationship between MLH3 mutations and MSI status.

**Useful For:** Testing for mutations in all 12 exons of the MLH3 gene

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics (ACMG) recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.


**MLYCD Gene, Full Gene Analysis**

**Clinical Information:** Malonyl-coenzyme A decarboxylase (MCD) deficiency is a rare autosomal recessive inborn error of fatty acid metabolism characterized by reduced activity of mitochondrial malonyl-CoA decarboxylase. This enzyme is responsible for conversion of intramitochondrial malonyl-CoA to acetyl-CoA and carbon dioxide. This leads to an accumulation of malonyl-CoA, which is a strong inhibitor of carnitine palmitoyltransferase-I (CPT-I), an enzyme active in beta-oxidation of fatty acids. The resulting effect is impairment of the breakdown of fatty acids. Isoforms of CPT-I have been found in skeletal and heart muscle, liver, and brain, and symptoms seem to correlate with the localization of these isoforms. The phenotype associated with MCD deficiency is variable, but may include developmental delay, seizures, hypotonia, metabolic acidosis, hypoglycemia, ketosis, and cardiomyopathy. The diagnosis of MCD deficiency is based on the findings of high urinary excretion of malonic acid and a mild increase in dicarboxylic acid. Acylcarnitine analysis by tandem mass spectrometry shows high blood levels of malonylcarnitine (C3DC), which can be detected by neonatal screening before the appearance of symptoms. Determination of MCD activity in cultured fibroblasts can confirm the diagnosis, although this testing is not currently clinically available in the United States. Mutations in the MLYCD gene are responsible for MCD deficiency. The MLYCD gene is located on chromosome 16 and has 5 coding exons. Several different mutations have been described including missense, nonsense, small insertions and deletions, as well as large genomic deletions.

**Useful For:** Confirmation of diagnosis of malonyl-CoA decarboxylase deficiency Carrier screening in cases where there is a family history of malonyl-CoA decarboxylase deficiency, but disease-causing mutations have not been identified in an affected individual

**Interpretation:** All detected alterations are evaluated according to American College of Medical
Genetics recommendations. (1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.


**MMRV Immune Status Profile, Serum**

**Clinical Information:** Measles: The measles virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1-4, mumps, respiratory syncytial virus (RSV), and metapneumovirus. The measles virus is among the most highly contagious infectious diseases among unvaccinated individuals and is transmitted through direct contact with aerosolized droplets or other respiratory secretions from infected individuals. Measles has an incubation period of approximately 8 to 12 days, which is followed by a prodromal phase of high fever, cough, coryza, conjunctivitis, and malaise. Koplik spots may also be apparent on the buccal mucosa and can last from 12 to 72 hours. (1) Following this phase, a maculopapular, erythematous rash develops beginning behind the ears and on the forehead and spreading centrifugally to involve the trunk and extremities. Immunocompromised individuals, pregnant women, and those with nutritional deficiencies are particularly at risk for serious complications following measles infection, which include pneumonia and central nervous system involvement. (1) Following implementation of the national measles vaccination program in 1963, the incidence of measles infection has fallen to fewer than 0.5 cases per 1,000,000 population and the virus is no longer considered endemic in the United States. Measles outbreaks continue to occur in the United States due to exposure of nonimmune individuals or those with waning immunity to infected travelers. The measles outbreak in 2011 throughout Western Europe emphasizes the persistence of the virus in the worldwide population and the continued need for national vaccination programs. (2) The diagnosis of measles infection is often based on clinical presentation alone. Screening for IgG-class antibodies to measles virus will aid in identifying nonimmune individuals.

Mumps: The mumps virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1-4, measles, RSV, and metapneumovirus. Mumps is highly infectious among unvaccinated individuals and is typically transmitted through inhalation of infected respiratory droplets or secretions. Following an approximately 2-week incubation period, symptom onset is typically acute with a prodrome of low-grade fever, headache, and malaise. (3,4) Painful enlargement of the salivary glands, the hallmark of mumps, occurs in approximately 60% to 70% of infections and in 95% of patients with symptoms. Testicular pain (orchiitis) occurs in approximately 15% to 30% of postpubertal men and abdominal pain (oophoritis) is found in 5% of postpubertal women. (3) Other complications include mumps-associated pancreatitis (<5% of cases) and central nervous system disease (meningitis <10% and encephalitis <1%). Widespread routine immunization of infants with attenuated mumps virus has dramatically decreased the number of reported mumps cases in the United States. However, outbreaks continue to occur, indicating persistence of the virus in the general population. Laboratory diagnosis of mumps is typically accomplished by detection of IgM- and IgG-class antibodies to the mumps virus. However, due to the widespread mumps vaccination program, in clinically suspected cases of acute mumps infection, serologic testing should be supplemented with virus isolation in culture or detection of viral nucleic acid by PCR in throat, saliva, or urine specimens. Rubella: Rubella (German or 3-day measles) is a member of the Togaviridae family and humans remain the only natural host for this virus. Transmission is typically through inhalation of infectious aerosolized respiratory droplets and the incubation period following exposure can range from 12 to 23 days. (5) Infection is generally mild and self-limited, and is characterized by a maculopapular rash beginning on the face and spreading to the trunk and extremities, fever, malaise, and lymphadenopathy. (6) Primary in utero rubella infections can lead to severe sequelae for the fetus, particularly if infection occurs within the first 4 months of
gestation. Congenital rubella syndrome is often associated with hearing loss and cardiovascular and ocular defects. The United States 2-dose measles, mumps, and rubella (MMR) vaccination program, which calls for vaccination of all children, leads to seroconversion in 95% of children following the first dose. A total of 4 cases of rubella were reported to the CDC in 2011 without any cases of congenital rubella syndrome. Due to the success of the national vaccination program, rubella is no longer considered endemic in the United States (www.cdc.gov/rubella). Immunity may, however, wane with age as approximately 80% to 90% of adults will show serologic evidence of immunity to rubella.

Varicella-Zoster Virus (VZV): VZV, a herpes virus, causes 2 distinct exanthematous (rash-associated) diseases: chickenpox (varicella) and shingles (herpes zoster). Chickenpox is a highly contagious though typically benign disease usually contracted during childhood. Chickenpox is characterized by a dermal vesiculopustular rash that develops in successive crops approximately 10 to 21 days following exposure. Although primary infection with VZV results in immunity and protection from subsequent infection, VZV remains latent within sensory dorsal root ganglia and upon reactivation, manifests as herpes zoster or shingles. During reactivation, the virus migrates along neural pathways to the skin, producing a unilateral rash, usually limited to a single dermatome. Shingles is an extremely painful condition typically occurring in older, nonimmune adults or those with waning immunity to VZV and in patients with impaired cellular immunity. Individuals at risk for severe complications following primary VZV infection include pregnant women, in whom the virus may spread through the placenta to the fetus, causing congenital disease in the infant. Additionally, immunosuppressed patients are at risk for developing severe VZV-related complications, which include cutaneous disseminated disease and visceral organ involvement. Serologic screening for IgG-class antibodies to VZV aids in identifying nonimmune individuals.

**Useful For:** Determination of immune status of individuals to measles, mumps, rubella, and varicella-zoster viruses (VZV) Documentation of previous infection with measles, mumps, rubella, or VZV in an individual without a previous record of immunization to these viruses

**Interpretation:** Positive Measles, Mumps, Varicella-Zoster Viruses (VZV): Antibody Index (AI) Value > or =1.1 Positive Rubella: AI Value > or =1.0 The reported Antibody Index (AI) value is for reference only. This is a qualitative test and the numeric value of the AI is not indicative of the amount of antibody present. AI values above the manufacturer recommended cutoff for this assay indicate that specific antibodies were detected, suggesting prior exposure or vaccination. The presence of detectable IgG-class antibodies to these viruses indicates prior exposure through infection or immunization. Individuals testing positive for IgG-class antibodies to measles, mumps, rubella, or VZV are considered immune. Equivocal Measles, Mumps, VZV: AI Value 0.9-1.0 Equivocal Rubella: AI Value 0.8-0.9 Submit an additional sample for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative Measles, Mumps, VZV: AI Value < or =0.8 Negative Rubella: AI Value < or =0.7 The absence of detectable IgG-class antibodies to measles, mumps, rubella, or VZV suggests no prior exposure to these viruses or the lack of a specific immune response to immunization.

**Reference Values:**

- Measles, Mumps and Varicella
  - Vaccinated: Positive (> or =1.1 AI)
  - Unvaccinated: Negative (< or =0.8 AI)
  - Reference values apply to all ages

- Rubella
  - Vaccinated: Positive (> or =1.0 AI)
  - Unvaccinated: Negative (< or =0.7 AI)
  - Reference values apply to all ages

MOC31
70505

**MOC-31 Immunostain, Technical Component Only**

**Clinical Information:** antigen stains tumors of epithelial origin, adenocarcinomas, papillary serous carcinoma, breast, lung, prostate, and cholangiocarcinoma, among others. MOC31 may be used as part of a panel of stains to rule-out mesothelioma and support the diagnosis of carcinoma.

**Useful For:** Marker of epithelial cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


MOLD1
81878

**Mold Panel**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with...
the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Molybdenum, Blood**

**Clinical Information:** Molybdenum is an essential trace element and a component of metalloflavoproteins. High concentrations are found in leafy vegetables and legumes. The recommended daily dietary allowance for molybdenum is 45 mcg for adults.(1) As an industrial metal, molybdenum is used in the manufacturing of steel alloys, lubricants, or pigments. Occupational exposure is generally from inhalation of dusts or fumes. The current threshold limit is 0.5 mg/m(2) for soluble compounds and 3 mg/m(2) (respirable fraction) for the metal and its insoluble compounds.(1) Oral absorption varies from 28% to 77%. Whole blood concentrations averaged 0.43 mcg/L (range 0.6-4.0 mcg/L) in unexposed individuals.(2) However, exposed adults averaged 2.7 mcg/L (range 1.2-4.8 mcg/L).(3) Once absorbed, molybdenum is primarily eliminated in the urine over 5 or more days.(4) Molybdenum deficiency can cause irritability, altered levels of consciousness, and a variety of biochemical abnormalities.(5) Toxicity can range from auditory and visual hallucinations, diarrhea, insomnia, painful extremities, and seizures.(6)

**Useful For:** Determining molybdenum toxicity

**Interpretation:** Normal blood concentrations are 0.6-4.0 ng/mL in unexposed individuals and 1.2-4.8 ng/mL in exposed individuals.(4)

**Reference Values:**

- <4 ng/mL (unexposed)
- <5 ng/mL (exposed)

**Clinical References:**

Molybdenum, Serum

Clinical Information: Molybdenum is an essential trace element found in the daily diet. It is a cofactor for some enzymes important in nitrogen metabolism (aldehyde dehydrogenase, xanthine oxidase, NADH dehydrogenase). Due to the wide distribution of molybdenum in the environment and particularly in plant materials, molybdenum deficiency is rare in adults with normal, diverse diets. Typical molybdenum intake in most geographic locations is between 45 and 90 mcg/day. Urine is the primary source of excretion, though excesses are sometimes excreted by the biliary route. Molybdenum deficiency associated with parenteral nutrition is indicated by symptoms such as stunted growth, reduced appetite, tachycardia, tachypnea, blindness and coma. These symptoms can be corrected by introducing molybdenum supplementation. Molybdenum cofactor disease is a severe genetic disorder that is due to defective mutations in the MOCS1, MOCS2, and GEPH genes. Molybdenum toxicity is rare and usually related to molybdenum mining exposure; however, it has been observed in cases of intake above 400 mcg/day. Molybdenum interferes with copper uptake; molybdenum toxicity is predominantly due to copper deficiency (hypochromic anemia and neutropenia) and inhibition of xanthine oxidase (uric acid accumulation). Serum molybdenum concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside, typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

Useful For: Monitoring of parenteral nutrition Monitoring metallic prosthetic implant wear As an indicator of molybdenum cofactor disease

Interpretation: Prosthesis wear is known to result in increased circulating concentrations of metal ions.(1 Serum concentrations above 10 ng/mL in a patient with molybdenum-based implant suggest significant prosthesis wear. Increased serum trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure. Serum molybdenum levels below 0.3 ng/mL indicate potential deficiency. Increased serum molybdenum may be seen in acute viral hepatitis, chronic active hepatitis, alcoholic liver disease, and other forms of liver inflammation.

Reference Values:
0.3-2.0 ng/mL


Monoamine Neurotransmitter Metabolites/Amines

Reference Values:
CSF Metabolite Age related reference ranges (values expressed in nmol/L)

5-Hydroxyindoleacetic acid (5HIAA)

<table>
<thead>
<tr>
<th>Age</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn 0-73 days</td>
<td>208-1159</td>
</tr>
<tr>
<td>Infant 73 days-6 months</td>
<td>179-711</td>
</tr>
<tr>
<td>Toddler 6 months-2 years</td>
<td>129-520</td>
</tr>
</tbody>
</table>
Monoclonal Gammopathy Monitoring, Serum

**Clinical Information:** This profile includes both total protein and protein electrophoresis. The serum proteins can be grouped into 5 fractions by protein electrophoresis: -Albumin, which represents almost two-thirds of the total serum protein -Alpha-1, composed primarily of alpha-1-antitrypsin (A1AT), an alph-1-acid glycoprotein -Alpha-2, composed primarily of alpha-2-macroglobulin and haptoglobin -Beta, composed primarily of transferrin and C3 -Gamma, composed primarily of immunoglobulins The concentration of these fractions and the electrophoretic pattern may be characteristic of diseases such as monoclonal gammopathies, A1AT deficiency disease, nephrotic syndrome, and inflammatory processes associated with infection, liver disease, and autoimmune diseases.

**Useful For:** Monitoring patients with monoclonal gammopathies This test is not recommended to screen or establish a first-time diagnosis for a monoclonal gammopathy

**Interpretation:** Monoclonal Gammopathies: A characteristic monoclonal band (M-spike) is often found on serum protein electrophoresis (SPE) in the gamma globulin region and, more rarely, in the beta or alpha-2 regions. The finding of an M-spike, restricted migration, or hypogammaglobulinemic SPE pattern is suggestive of a possible monoclonal protein. Immunoaffinity purification followed by matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) is performed to identify any immunoglobulin heavy and light chains present. -A monoclonal IgG or IgA of greater than 3 g/dL is consistent with multiple myeloma (MM). -A monoclonal IgG or IgA of less than 3 g/dL may be consistent with monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis, early or treated myeloma, as well as a number of other monoclonal gammopathies. -A monoclonal IgM of greater than 3 g/dL is consistent with macroglobulinaemia. -The initial identification of a serum M-spike greater than 1.5 g/dL on SPEP should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -The initial identification of an IgM, IgA, or IgG M-spike greater than 4 g/dL, greater than 5 g/dL, and greater than 6 g/dL respectively, should be followed by VISCS / Viscosity, Serum. After the initial identification of an M-spike, quantitation of the M-spike on follow-up SPE can be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the beta region (most commonly an IgA or an IgM) quantitative immunoglobulin levels may be more a useful tool to follow the monoclonal protein level than SPE. A decrease or increase of the M-spike that is greater than 0.5 g/dL is considered a significant change. Patients suspected of having a monoclonal gammopathy may have normal SPE patterns. Approximately 11% of patients with MM have a completely normal SPE, with the monoclonal protein only identified by MALDI-TOF MS.

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  Page 1528
Approximately 8% of MM patients have hypogammaglobulinemia without a quantifiable M-spike on SPE, but identified by MALDI-TOF MS. Accordingly, a normal serum SPE does not rule out the disease and should not be used to screen for the disorder. SMOGA / Monoclonal Gammopathy Screen, Serum, which includes MALDI-TOF MS and serum free light chains, conforms to the International Myeloma Working Group (IMWG) guidelines for screening and should be performed if there is clinical suspicion. Other Abnormal SPE Findings: -A qualitatively normal but elevated gamma fraction (polyclonal hypergammaglobulinemia) is consistent with infection, liver disease, or autoimmune disease. A depressed gamma fraction (hypogammaglobulinemia) is consistent with immune deficiency and can also be associated with primary amyloidosis or nephrotic syndrome. A decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.1 g/dL), and decreased gamma fraction (<1 g/dL) is consistent with nephritic syndrome and, when seen in an adult older than 40 years, should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. In the hereditary deficiency of a protein (eg, agammaglobulinemia, alpha-1-antitrypsin [A1AT] deficiency, hypoalbuminemia), the affected fraction is faint or absent. An absent alpha-1 fraction is consistent with A1AT deficiency disease and should be followed by a quantitative A1AT assay (AAT / Alpha-1-Antitrypsin, Serum).

Reference Values:
TOTAL PROTEIN:
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients that are <12 months of age.

PROTEIN ELECTROPHORESIS:
Albumin: 3.4-4.7 g/dL
Alpha 1-Globulin: 0.1-0.3 g/dL
Alpha 2-Globulin: 0.6-1.0 g/dL
Beta-Globulin: 0.7-1.2 g/dL
Gamma-Globulin: 0.6-1.6 g/dL
An interpretive comment is provided.
Reference values have not been established for patients that are <16 years of age.


SMOGA 603223
Monoclonal Gammopathy Screen, Serum
Clinical Information: Monoclonal proteins are markers of plasma cell proliferative disorders. The International Myeloma Working Group guidelines state that to adequately screen for a monoclonal protein, serum protein electrophoresis (SPE), immunofixation electrophoresis, and a serum free light chain should all be used. If amyloidosis is suspected, a 24 hour urine monoclonal protein study should be performed. The detection of M-proteins by matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) has shown to be more analytically and clinically sensitive than immunofixation. In addition, the MALDI-TOF method can detect glycosylated light chains that have been demonstrated to be a risk factor for amyloidosis (AL). This expanded monoclonal protein testing panel provides the highest diagnostic sensitivity for the monoclonal light chain diseases such as primary amyloidosis and light chain deposition disease—disorders that often do not have serum monoclonal proteins in high enough concentration to be detected and quantitated by SPE. The free light-chain (FLC) assay is specific for free kappa and lambda light chains and does not recognize light chains bound to intact immunoglobulin. Monoclonal gammopathies may be present in a wide spectrum of diseases that include malignancies of plasma cells or B lymphocytes (multiple myeloma: MM, macroglobulinemia, plasmacytoma, B-cell lymphoma), disorders of monoclonal protein structure (primary amyloid, light chain deposition disease, cryoglobulinemia), and apparently benign, premalignant conditions (monoclonal gammopathy of undetermined significance: MGUS, smoldering MM). While the identification of the monoclonal gammapathy is a laboratory diagnosis, the specific clinical diagnosis is...
dependent on a number of other laboratory and clinical assessments. If a monoclonal protein pattern is detected by MALDI-TOF MS, immunofixation electrophoresis (IFE), or FLC, a diagnosis of a monoclonal gammopathy is established. Once a monoclonal gammopathy has been diagnosed, the size of the clonal abnormality can be monitored by SPE or FLC and, in some instances, by quantitative immunoglobulins. In addition, if the patient is asymptomatic and has a diagnosis of MGUS, the monoclonal gammopathy screen provides the information (size of M-spike, monoclonal protein isotype, FLC K/L ratio) needed for a MGUS progression risk assessment (see Interpretation).

Useful For: Screening and diagnosis of monoclonal gammopathies including analysis of free light chains Assessing the risk of progression from monoclonal gammopathy of undetermined significance to multiple myeloma

Interpretation: Monoclonal Gammopathies: -A characteristic monoclonal band (M-spike) is often found on serum protein electrophoresis (SPE) in the gamma globulin region and, more rarely, in the beta or alpha-2 regions. The finding of an M-spike, restricted migration, or hypogammaglobulinemic SPE pattern is suggestive of a possible monoclonal protein. Matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) is performed to identify any immunoglobulin heavy and light chains present. -A monoclonal IgG or IgA of greater than 3 g/dL is consistent with multiple myeloma (MM). -A monoclonal IgG or IgA of less than 3 g/dL may be consistent with monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis, early or treated myeloma, as well as a number of other monoclonal gammopathies. -A monoclonal IgM of greater than 3 g/dL is consistent with macroglobulinemia. -An abnormal serum free light chain (FLC) K/L ratio in the presence of a normal MALDI-TOF MS suggests a monoclonal light chain process and should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -The initial identification of a serum M-spike greater than 1.5 g/dL on SPE should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -The initial identification of an IgM, IgA, or IgG M-spike greater than 4 g/dL, greater than 5 g/dL, and greater than 6 g/dL, respectively, a VISCS / Viscosity, Serum should be tested to rule out hyperviscosity syndrome. After the initial identification of a monoclonal band, quantitation of the M-spike on follow-up SPE can be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the beta region (most commonly an IgA or an IgM) quantitative immunoglobulin levels may be a more useful tool to follow the monoclonal protein level than SPE. A decrease or increase of the M-spike that is greater than 0.5 g/dL is considered a significant change. Patients with monoclonal light chain diseases who have no serum or urine M-spike may be monitored with the serum FLC value. Patients suspected of having a monoclonal gammopathy may have normal serum SPE patterns. Approximately 11% of patients with MM have a completely normal serum SPE, with the monoclonal protein only identified by MALDI-TOF MS. Approximately 8% of MM patients have hypogammaglobulinemia without a quantifiable M-spike on SPE but identified by MALDI-TOF MS or FLC. Accordingly, a normal serum SPE does not rule out the disease and SPE alone should not be used to screen for the disorder if the clinical suspicion is high. MGUS Prognosis: -Low-risk MGUS patients are defined as having an M-spike of less than 1.5 g/dL, IgG monoclonal protein, and a normal FLC K/L ratio (0.25-1.65), and these patients have a lifetime risk of progression to MM of less than 5%. -High-risk MGUS patients (M-spike >1.5, IgA or IgM, abnormal FLC ratio) have a lifetime risk of progression to MM of 60%. Other Abnormal SPE Findings: -A qualitatively normal but elevated gamma fraction (polyclonal hypergammaglobulinemia) is consistent with infection, liver disease, or autoimmune disease. -A depressed gamma fraction (hypogammaglobulinemia) is consistent with immune deficiency and can also be associated with primary amyloidosis or nephrotic syndrome. -A decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.1 g/dL), and decreased gamma fraction (<1 g/dL) is consistent with nephrotic syndrome and, when seen in an adult older than 40 years, should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -In the hereditary deficiency of a protein (e.g., agammaglobulinemia, alpha-1-antitrypsin [A1AT] deficiency, hypoalbuminemia), the affected fraction is faint or absent. -An absent alpha-1 fraction is consistent with A1AT deficiency disease and should be followed by a quantitative A1AT assay (AAT / Alpha-1-Antitrypsin, Serum).

Reference Values:
TOTAL PROTEIN:
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients that are <12 months of age.

PROTEIN ELECTROPHORESIS
Albumin: 3.4-4.7 g/dL
Alpha-1-globulin: 0.1-0.3 g/dL
Alpha-2-globulin: 0.6-1.0 g/dL
Beta-globulin: 0.7-1.2 g/dL
Gamma-globulin: 0.6-1.6 g/dL

An interpretive comment is provided with the report. Reference values have not been established for patients that are <16 years of age.

M-PROTEIN ISOTYPE MALDI-TOF MS
No monoclonal protein detected

KAPPA-FREE LIGHT CHAIN
0.33-1.94 mg/dL

LAMBDA-FREE LIGHT CHAIN
0.57-2.63 mg/dL

KAPPA/LAMBDA-FREE LIGHT-CHAIN RATIO
0.26-1.65

Clinical References:

Monoclonal Protein Study, 24 Hour, Urine

Clinical Information: Urine proteins can be grouped into 5 fractions by protein electrophoresis:
- Albumin
- Alpha-1
- Alpha-2
- Beta-globulin
- Gamma-globulin

The urine total protein concentration, the electrophoretic pattern, and the presence of a monoclonal immunoglobulin light chain may be characteristic of monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, and light chain deposition disease. The following algorithms are available in Special Instructions:
- Laboratory Approach to the Diagnosis of Amyloidosis
- Laboratory Screening Tests for Suspected Multiple Myeloma

Useful For: Monitoring patients with monoclonal gammopathies using 24-hour urine specimens

Interpretation: A characteristic monoclonal band (M-spike) is often found in the urine of patients with monoclonal gammopathies. The initial identification of an M-spike or an area of restricted migration is followed by immunofixation to identify the immunoglobulin heavy chain and/or light chain. Immunoglobulin free light chains as well as heavy chain fragments may be seen in the urine of patients with monoclonal gammopathies. The presence of a monoclonal light chain M-spike of greater than 1 g/24 hours is consistent with a diagnosis of multiple myeloma or macroglobulinemia. The presence of a small amount of monoclonal light chain and proteinuria (total protein >3 g/24 hrs) that is predominantly albumin is consistent with primary systemic amyloidosis (AL) or light chain deposition disease (LCDD). Because patients with AL or LCDD may have elevated urinary protein without an identifiable M-spike, urine protein electrophoresis is not considered an adequate screen for these disorders and immunofixation is also recommended.

Reference Values:
PROTEIN, TOTAL
<229 mg/24 hours
   Reference values have not been established for patients <18 years of age.
   Reference value applies to 24-hour collection.

ELECTROPHORESIS, PROTEIN
The following fractions, if present, will be reported as a percent of the protein, total.
   Albumin
   Alpha-1-globulin
   Alpha-2-globulin
   Beta-globulin
   Gamma globulin

Clinical References: Kyle RA, Katzmann JA, Lust JA, Dispenzieri A: Clinical indications and
   applications of electrophoresis and immunofixation. In Manual of Clinical Laboratory Immunology. Sixth

MPSEX 87997
Monoclonal Protein Study, Expanded Panel, Serum

Clinical Information: Monoclonal proteins are markers of plasma cell proliferative disorders. It has
   been recommended that serum and urine protein electrophoresis (PEL) and immunofixation
   electrophoresis (IFE) be performed as the diagnostic algorithm (eg, MPSS / Monoclonal Protein Study,
   Serum and MPSU / Monoclonal Protein Study, 24 Hour, Urine): A monoclonal band (M-spike) on serum
   and/or urine PEL identifies a monoclonal process and quantitates the abnormality. IFE characterizes the
   type of monoclonal protein (gamma, alpha, mu, delta, or epsilon heavy chain; kappa [K] or lambda [L]
   light chain). IFE is also more sensitive than PEL for detecting small abnormalities that may be present in
diseases such as light chain multiple myeloma, oligosecretory myeloma, and plasmacytomas. With the
addition of the serum free light chain (FLC) assay, the expanded monoclonal protein study provides even
more diagnostic sensitivity for the monoclonal light chain diseases such as primary amyloid and light
chain deposition disease--disorders that often do not have serum monoclonal proteins in high enough
concentration to be detected and quantitated by PEL. The FLC assay is specific for free kappa and lambda
light chains and does not recognize light chains bound to intact immunoglobulin. Importantly, the addition
of the serum FLC assay to serum PEL and IFE makes the serum diagnostic studies sufficiently sensitive
so that urine specimens are no longer required as part of initial diagnostic studies. Monoclonal
   gammopathies may be present in a wide spectrum of diseases that include malignancies of plasma cells or
   B lymphocytes (multiple myeloma: MM, macroglobulinemia, plasmacytoma, B-cell lymphoma),
disorders of monoclonal protein structure (primary amyloid, light chain deposition disease,
cryoglobulinemia), and apparently benign, premalignant conditions (monoclonal gammopathy of
   undetermined significance: MGUS, smoldering MM). While the identification of the monoclonal
   gammopathy is a laboratory diagnosis, the specific clinical diagnosis is dependent on a number of other
laboratory and clinical assessments. If a monoclonal protein pattern is detected by IFE or FLC, a
diagnosis of a monoclonal gammopathy is established. Once a monoclonal gammopathy has been
diagnosed, the size of the clonal abnormality can be monitored by PEL and/or FLC and in some instances
by quantitative immunoglobulins. In addition, if the patient is asymptomatic and has a diagnosis of
MGUS, the expanded monoclonal protein study panel provides the information (size of M-spike,
monoclonal protein isotype, FLC K/L ratio) needed for a MGUS progression risk assessment (see
Interpretation).

Useful For: Diagnosis of monoclonal gammopathies Eliminating the need for urine monoclonal studies
   as a part of initial diagnostic studies (ie, rule-out monoclonal gammopathy) Assessing risk of progression
from monoclonal gammopathy of undetermined significance to multiple myeloma

Interpretation: Monoclonal Gammopathies: A characteristic monoclonal band (M-spike) is often
found on protein electrophoresis (PEL) in the gamma globulin region and, more rarely, in the beta or
alpha-2 regions. The finding of an M-spike, restricted migration, or hypogamaglobulinemic PEL pattern
is suggestive of a possible monoclonal protein. Immunofixation electrophoresis (IFE) is performed to
identify the immunoglobulin heavy chain and/or light chain. A monoclonal IgG or IgA of greater than 3
g/dL is consistent with multiple myeloma (MM). A monoclonal IgG or IgA of less than 3 g/dL may be consistent with monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis, early or treated myeloma, as well as a number of other monoclonal gammopathies. A monoclonal IgM of greater than 3 g/dL is consistent with macroglobulinemia. An abnormal serum free light chain (FLC) K/L ratio in the presence of a normal IFE suggests a monoclonal light chain process and should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. The initial identification of a serum M-spike greater than 1.5 g/dL on PEL should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. The initial identification of an IgM, IgA, or IgG M-spike greater than 4 g/dL, greater than 5 g/dL, and greater than 6 g/dL, respectively, should be followed by VISCIS / Viscosity, Serum. After the initial identification of a monoclonal band, quantitation of the M-spike on follow-up PEL can be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the beta region (most commonly an IgA or an IgM) quantitative immunoglobulin levels may be more a useful tool to follow the monoclonal protein level than PEL. A decrease or increase of the M-spike that is greater than 0.5 g/dL is considered a significant change. Patients with monoclonal light chain diseases who have no serum or urine M-spike may be monitored with the serum FLC value. Patients suspected of having a monoclonal gammopathy may have normal serum PEL patterns. Approximately 11% of patients with MM have a completely normal serum PEL, with the monoclonal protein only identified by IFE. Approximately 8% of MM patients have hypogammaglobulinemia without a quantifiable M-spike on PEL but identified by IFE and/or FLC. Accordingly, a normal serum PEL does not rule out the disease and PEL alone should not be used to screen for the disorder if the clinical suspicion is high. MGUS Prognosis: Low-risk MGUS patients are defined as having an M-spike of less than 1.5 g/dL, IgG monoclonal protein, and a normal FLC K/L ratio (0.25-1.65), and these patients have a lifetime risk of progression to MM of less than 5%. High-risk MGUS patients (M-spike >1.5, IgA or IgM, abnormal FLC ratio) have a lifetime risk of progression to MM of 60%. Other Abnormal PEL Findings: A qualitatively normal but elevated gamma fraction (polyclonal hypergammaglobulinemia) is consistent with infection, liver disease, or autoimmune disease. A depressed gamma fraction (hypogammaglobulinemia) is consistent with immune deficiency and can also be associated with primary amyloidosis or nephrotic syndrome. A decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.2 g/dL), and decreased gamma fraction (<1 g/dL) is consistent with nephritic syndrome and, when seen in an adult older than 40 years, should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. In the hereditary deficiency of a protein (eg, agammaglobulinemia, alpha-1-antitrypsin [A1AT] deficiency, hypoalbuminemia), the affected fraction is faint or absent. An absent alpha-1 fraction is consistent with A1AT deficiency disease and should be followed by a quantitative A1AT assay (AAT / Alpha-1-Antitrypsin, Serum).

Reference Values:
PROTEIN, TOTAL
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients that are <12 months of age.

PROTEIN ELECTROPHORESIS
Albumin: 3.4-4.7 g/dL
Alpha-1-globulin: 0.1-0.3 g/dL
Alpha-2-globulin: 0.6-1.0 g/dL
Beta-globulin: 0.7-1.2 g/dL
Gamma-globulin: 0.6-1.6 g/dL
An interpretive comment is provided with the report.

IMMUNOFIXATION
No monoclonal protein detected

KAPPA-FREE LIGHT CHAIN
0.33-1.94 mg/dL

LAMBDA-FREE LIGHT CHAIN
0.57-2.63 mg/dL

KAPPA/LAMBDA-FREE LIGHT-CHAIN RATIO
0.26-1.65

Monoclonal Protein Study, Random, Urine
Clinical Information: Urine proteins can be grouped into 5 fractions by protein electrophoresis: -Albumin -Alpha-1 -Alpha-2 -Beta-globulin -Gamma-globulin The urine total protein concentration, the electrophoretic pattern, and the presence of a monoclonal immunoglobulin light chain may be characteristic of monoclonal gammopathies such as multiple myeloma, primary systemic amyloidosis, and light-chain deposition disease. The following algorithms are available in Special Instructions: -Laboratory Approach to the Diagnosis of Amyloidosis -Laboratory Screening Tests for Suspected Multiple Myeloma

Useful For: Diagnosing monoclonal gammopathies

Interpretation: A characteristic monoclonal band (M-spike) is often found in the urine of patients with monoclonal gammopathies. The initial identification of an M-spike or an area of restricted migration is followed by immunofixation to identify the immunoglobulin heavy chain and/or light chain. Immunoglobulin free light chains as well as heavy chain fragments may be seen in the urine of patients with monoclonal gammopathies. The presence of a monoclonal light-chain M-spike of greater than 1 g/24 hours is consistent with a diagnosis of multiple myeloma or macroglobulinemia. The presence of a small amount of monoclonal light chain and proteinuria (total protein >3 g/24 hrs) that is predominantly albumin is consistent with primary systemic amyloidosis (AL) or light-chain deposition disease (LCDD). Because patients with AL or LCDD may have elevated urinary protein without an identifiable M-spike, urine protein electrophoresis is not considered an adequate screen for these disorders and immunofixation is also recommended.

Reference Values:
PROTEIN, TOTAL
No reference values apply to random urine.
ELECTROPHORESIS, PROTEIN
The following fractions, if present, will be reported as a percent of the total protein:
Albumin
Alpha-1-globulin
Alpha-2-globulin
Beta-globulin
Gamma-globulin


Monoclonal Protein Study, Serum
Clinical Information: Serum proteins can be grouped into 5 fractions by protein electrophoresis: -Albumin, which represents almost two-thirds of the total serum protein -Alpha-1, composed primarily of alpha-1-antitrypsin (A1AT), an alpha-1-acid glycoprotein -Alpha-2, composed primarily of alpha-2-macroglobulin and haptoglobin -Beta, composed primarily of transferrin and complement C3 -Gamma, composed primarily of immunoglobulins (Ig) The concentration of these fractions and the electrophoretic pattern may be characteristic of diseases such as monoclonal gammopathies, A1AT

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deficiency disease, nephrotic syndrome, and inflammatory processes associated with infection, liver
disease, and autoimmune diseases. The following algorithms are available in Special Instructions:
-Laboratory Approach to the Diagnosis of Amyloidosis -Laboratory Screening Tests for Suspected
Multiple Myeloma

Useful For: Diagnosis of monoclonal gammopathies, when used in conjunction with urine
monoclonal studies Monitoring patients with monoclonal gammopathies Protein electrophoresis alone is
not considered an adequate screen for monoclonal gammopathies

Interpretation: Monoclonal Gammopathies: -A characteristic monoclonal band (M-spike) is often
found on protein electrophoresis (PEL) in the gamma globulin region and, more rarely, in the beta or
alpha-2 regions. The finding of an M-spike, restricted migration, or hypogammaglobulinemic PEL
pattern is suggestive of a possible monoclonal protein and should be followed by MPSU / Monoclonal
Protein Study, 24 Hour, Urine, which includes immunofixation (IF), to identify the immunoglobulin
(Ig) heavy chain and/or light chain. -A monoclonal IgG or IgA >3 g/dL is consistent with multiple
myeloma (MM). -A monoclonal IgG or IgA <3 g/dL may be consistent with monoclonal gammopathy
of undetermined significance (MGUS), primary systemic amyloidosis, early or treated myeloma, as well
as a number of other monoclonal gammopathies. -A monoclonal IgM >3 g/dL is consistent with
macroglobulinemia. -The initial identification of a serum M-spike >1.5 g/dL on PEL should be followed
by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -The initial identification of an IgM, IgA, or
IgG M-spike >4 g/dL, >5 g/dL, and >6 g/dL respectively, should be followed by VISCS / Viscosity,
Serum. -After the initial identification of an M-spike, quantitation of the M-spike on follow-up PEL can
be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the
beta region (most commonly an IgA or an IgM) quantitative immunoglobulin levels may be more a
useful tool to follow the monoclonal protein level than PEL. A decrease or increase of the M-spike that
is >0.5 g/dL is considered a significant change. -Patients suspected of having a monoclonal
gammopathy may have normal serum PEL patterns. Approximately 11% of patients with MM have a
completely normal serum PEL, with the monoclonal protein only identified by IF. Approximately 8% of
MM patients have hypogammaglobulinemia without a quantifiable M-spike on PEL but identified by
IF. Accordingly, a normal serum PEL does not rule out the disease and PEL should not be used to
screen for the disorder. MPSS / Monoclonal Protein Study, Serum, which includes IF, should be done to
screen if the clinical suspicion is high. Other Abnormal PEL Findings: -A qualitatively normal but
elevated gamma fraction (polyclonal hypergammaglobulinemia) is consistent with infection, liver
disease, or autoimmune disease. -A depressed gamma fraction (hypogammaglobulinemia) is consistent
with immune deficiency and can also be associated with primary amyloidosis or nephrotic syndrome.
-A decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.2 g/dL), and decreased gamma fraction
(<1 g/dL) is consistent with nephritic syndrome and, when seen in an adult older than 40 years, should
be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -In the hereditary deficiency of a
protein (eg. agammaglobulinemia, alpha-1-antitrypsin [A1AT] deficiency, hypoalbuminemia), the
affected fraction is faint or absent. -An absent alpha-1 fraction is consistent with A1AT deficiency
disease and should be followed by a quantitative A1AT assay (AAT / Alpha-1-Antitrypsin, Serum).

Reference Values:

PROTEIN, TOTAL
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients that are <12 months of age.

PROTEIN ELECTROPHORESIS
Albumin: 3.4-4.7 g/dL
Alpha-1-globulin: 0.1-0.3 g/dL
Alpha-2-globulin: 0.6-1.0 g/dL
Beta-globulin: 0.7-1.2 g/dL
Gamma-globulin: 0.6-1.6 g/dL

An interpretive comment is provided with the report.
Reference values have not been established for patients that are <16 years of age.

IMMUNOFIXATION
No monoclonal protein detected

MAAPC 113368
Morph Analysis, Automated (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

MAMPC 113369
Morph Analysis, Manual (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

MANPC 601983
Morph Analysis, Nerve (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

FMORS 75144
Morphine Confirmation, Serum
Reference Values:
Report Limit: 1 ng/mL
Reference Range: 21 ng/mL to 65 ng/mL

SPSM 9184
Morphology Evaluation (Special Smear)
Clinical Information: Under normal conditions, the morphology and proportion of each blood cell type is fairly consistent in corresponding age groups. The morphology and proportion of each blood cell type may change in various hematologic diseases. Differential leukocyte count and special smear evaluation is helpful in revealing the changes in morphology or proportion of each cell type in the peripheral blood.
Useful For: Detecting disease states or syndromes of the white blood cells, red blood cells, or platelet cell lines of a patient's peripheral blood
Interpretation: The laboratory will provide an interpretive report of percentage of white cells and, if appropriate, evaluation of white cells, red cells, and platelets.
Reference Values:
An interpretive report will be provided.

MSPP 82845
Mosquito Species, IgE
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>1</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>2</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>4</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>&gt; or ≥100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

*Reference values apply to all ages.*


**Moth, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm
sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Motilin, Plasma or Serum**

**Clinical Information:** Motilin is a 22 amino acid peptide produced primarily by the enterochromaffin cells (EC2 or M cells) in the intestine, duodenum and the jejunum. It is absent from the stomach and colon. Motilin accelerates gastric emptying and colonic motor activity. Motilin also stimulates the feeding response. It has no structural similarities with other gastrointestinal peptides. Motilin secretion can be stimulated by acid and a fat-rich meal. Motilin can increase the secretion of pepsin and causes increased intra-gastric pressure. Motilin also stimulates lower esophageal sphincter contraction. Motilin levels are suppressed by Calcitonin. Motilin has a short half-life of approximately five minutes.

**Reference Values:**

Up to 446 pg/mL

This test was developed and its performance characteristics determined by Inter Science Institute. It has not been cleared or approved by the US Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

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**Motor Neuron Disease Panel (Bill Only)**

**Reference Values:**

This test is for billing purposes only.

This is not an orderable test.

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**Motor Neuropathy Panel**

**Reference Values:**

<table>
<thead>
<tr>
<th>0 â€“ 30 days</th>
<th>1 â€“ 7 mg/dL</th>
<th>9 â€“ 11 months</th>
<th>16 â€“ 83 mg/dL</th>
</tr>
</thead>
</table>

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Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Immunoglobulin G

0–30 days: 611–1542 mg/dL 11 months: 282–1026 mg/dL
1 month: 241–870 mg/dL 1 year: 331–1164 mg/dL
2 months: 198–577 mg/dL 2 years: 407–1009 mg/dL
3 months: 169–558 mg/dL 3 years: 423–1097 mg/dL
4 months: 188–536 mg/dL 4 years: 444–1187 mg/dL
5 months: 165–781 mg/dL 5–7 years: 608–1229 mg/dL
6 months: 206–676 mg/dL 8–9 years: 584–1509 mg/dL
7–8 months: 208–868 mg/dL 10 years and older: 768–1632 mg/dL

Immunoglobulin M

0–30 days: 0–24 mg/dL 11 months: 39–142 mg/dL
1 month: 19–83 mg/dL 1 year: 41–164 mg/dL
2 months: 16–100 mg/dL 2 years: 46–160 mg/dL
3 months: 23–85 mg/dL 3 years: 45–190 mg/dL
4 months: 26–96 mg/dL 4 years: 41–186 mg/dL
5 months: 31–103 mg/dL 5–7 years: 46–197 mg/dL
6 months: 33–97 mg/dL 8–9 years: 49–230 mg/dL
7–8 months: 32–120 mg/dL 10 years and older: 35–263 mg/dL

Myelin Associated Glycoprotein (MAG) Antibody, IgM

Less than 1000 TU An elevated IgM antibody concentration greater than 999 TU against myelin-associated glycoprotein (MAG) suggests active demyelination in peripheral neuropathy. A normal concentration (less than 999 TU) generally rules out an anti-MAG antibody-associated peripheral neuropathy. TU= Titer Units

Sulfate-3-Glucuronyl Paragloboside (SGPG) Antibody, IgM

Less than 1.00 IU The majority of sulfate-3-glucuronyl paragloboside (SGPG) IgM-positive sera will show reactivity against MAG. Patients who are SGPG IgM positive and MAG IgM negative may have multi-focal motor neuropathy with conduction block.
**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>
| 6     | > or =100 | Strongly positive Reference values apply to all ages.


**Mouse Epithelium, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease.
and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**Reference values apply to all ages.**


**Mouse Serum Protein, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
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</tbody>
</table>

**Current as of October 11, 2018 2:20 pm CDT**
MOUP 82795

Mouse Urine Protein, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<table>
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<tr>
<th>Class</th>
<th>IgE kU/L</th>
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<tr>
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<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Movement Disorder Evaluation, Serum

Clinical Information: Autoimmune movement disorders encapsulate a large and diverse group of neurologic disorders occurring either in isolation or accompanying more diffuse autoimmune encephalitic illnesses. The full range of movement phenomena has been described and, as they often occur in adults, many of the presentations can mimic neurodegenerative disorders, such as autoimmune chorea mimicking Huntington disease. Disorders may be ataxic, hypokinetic (parkinsonism), or hyperkinetic (myoclonus, chorea other dyskinetic disorders). The autoantibody targets are diverse and include neuronal surface proteins such as leucine-rich, glioma-inactivated 1 (LGI1), as well as antibodies reactive with intracellular antigens (such as PCA-1) that are markers of a central nervous system process mediated by CD8+ cytotoxic T cells. In some instances (such as Purkinje cell cytoplasmic antibody-1 (PCA-1) autoimmunity), antibodies detected in serum and cerebrospinal fluid can be indicative of a paraneoplastic cause, and may direct the cancer search. In other instances (such as 65kDa isoform of glutamic acid decarboxylase [GAD65] autoimmunity), a paraneoplastic cause is very unlikely, and early treatment with immunotherapy may promote improvement or recovery.

Useful For: Evaluating patients with suspected paraneoplastic or other autoimmune movement disorders including patients with ataxia, chorea, dyskinesias, myoclonus, parkinsonism, and stiff-person spectrum

Interpretation: A positive antibody result is consistent with a diagnosis of an autoimmune movement disorder. A search for cancer may be indicated, depending on the antibody profile. A trial of immune therapy may bring about improvement in neurological symptoms.

Reference Values:

<table>
<thead>
<tr>
<th>Test ID</th>
<th>Reporting Name</th>
<th>Reference Value</th>
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<td>AChR Ganglionic Neuronal Ab, S</td>
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</tr>
<tr>
<td>AMPHS</td>
<td>Amphiphysin Ab, S</td>
<td></td>
</tr>
<tr>
<td>AGN1S</td>
<td>Anti-Glia Nuclear Ab, Type 1</td>
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</tr>
<tr>
<td>ANN1S</td>
<td>Anti-Neuronal Nuclear Ab, Type 1</td>
<td></td>
</tr>
<tr>
<td>ANN2S</td>
<td>Anti-Neuronal Nuclear Ab, Type 2</td>
<td></td>
</tr>
<tr>
<td>ANN3S</td>
<td>Anti-Neuronal Nuclear Ab, Type 3</td>
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</tr>
<tr>
<td>CS2CS</td>
<td>CASPR2-IgG CBA, S</td>
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<tr>
<td>CRMS</td>
<td>CRMP-5-IgG, S</td>
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<tr>
<td>CRMWS</td>
<td>CRMP-5-IgG Western Blot, S</td>
<td>Negative</td>
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<tr>
<td>DPPIS</td>
<td>DPPX Ab IFA, S</td>
<td>Negative</td>
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<tr>
<td>GD65S</td>
<td>GAD65 Ab Assay, S</td>
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</tr>
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<td>LG1CS</td>
<td>LGI1-IgG CBA, S</td>
<td>Negative</td>
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<tr>
<td>GL1IS</td>
<td>mGluR1 Ab IFA, S</td>
<td>Negative</td>
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<tr>
<td>VGKC</td>
<td>Neuronal (V-G) K+ Channel Ab, S</td>
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<td>NMDCS</td>
<td>NMDA-R Ab CBA, S</td>
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<tr>
<td>CCN</td>
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<td>CCPQ</td>
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<td>Purkinje Cell Cytoplasmic Ab Type 1</td>
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<tr>
<td>PCAB2</td>
<td>Purkinje Cell Cytoplasmic Ab Type 2</td>
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### Clinical References:


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**Movement Disorder Evaluation, Spinal Fluid**

**Clinical Information:** Autoimmune movement disorders encapsulate a large and diverse group of neurologic disorders occurring either in isolation or accompanying more diffuse autoimmune encephalitic illnesses. The full range of movement phenomena has been described and, as they often occur in adults, many of the presentations can mimic neurodegenerative disorders, such as autoimmune chorea mimicking Huntington disease. Disorders may be ataxic, hypokinetic (parkinsonism), or hyperkinetic (myoclonus, chorea other dyskinetic disorders). The autoantibody targets are diverse and include neuronal surface proteins such as leucine-rich, glioma-inactivated 1 (LGI1), as well as antibodies reactive with intracellular antigens (such as PCA-1) that are markers of a central nervous system process mediated by CD8+ cytotoxic T cells. In some instances (such as Purkinje cell cytoplasmic antibody-1 (PCA-1) autoimmunity), antibodies detected in serum and cerebrospinal fluid can be indicative of a paraneoplastic cause, and may direct the cancer search. In other instances (such as 65 kDa isoform of glutamic acid decarboxylase [GAD65] autoimmunity), a paraneoplastic cause is very unlikely, and early treatment with immunotherapy may promote improvement or recovery.

**Useful For:** Evaluating patients with suspected paraneoplastic or other autoimmune movement disorders including patients with ataxia, chorea, dyskinesias, myoclonus, parkinsonism, and stiff-person spectrum.

**Interpretation:** A positive antibody result is consistent with a diagnosis of an autoimmune movement disorder. A search for cancer may be indicated, depending on the antibody profile. A trial of immune therapy may bring about improvement in neurological symptoms.

**Reference Values:**

<table>
<thead>
<tr>
<th>Test ID</th>
<th>Reporting Name</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPHC</td>
<td>Amphiphysin Ab</td>
<td>Negative</td>
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</tbody>
</table>

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**Reflex Information:**

<table>
<thead>
<tr>
<th>Test ID</th>
<th>Reporting Name</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABLOT</td>
<td>Amphiphysin Western Blot</td>
<td>Negative</td>
</tr>
<tr>
<td>AMPIS</td>
<td>AMPA-R Ab IF Titer Assay</td>
<td>Negative</td>
</tr>
<tr>
<td>AMPCS</td>
<td>AMPA-R Ab CBA</td>
<td>Negative</td>
</tr>
<tr>
<td>DPPCS</td>
<td>DPPX Ab CBA</td>
<td>Negative</td>
</tr>
<tr>
<td>DPPTS</td>
<td>DPPX Ab IFA Titer</td>
<td>Negative</td>
</tr>
<tr>
<td>GABCS</td>
<td>GABA-B-R Ab CBA</td>
<td>Negative</td>
</tr>
<tr>
<td>GABIS</td>
<td>GABA-B-R Ab IF Titer Assay</td>
<td>Negative</td>
</tr>
<tr>
<td>GL1CS</td>
<td>mGluR1 Ab CBA</td>
<td>Negative</td>
</tr>
<tr>
<td>GL1TS</td>
<td>mGluR1 Ab IFA Titer</td>
<td>Negative</td>
</tr>
<tr>
<td>NMDIS</td>
<td>NMDA-R Ab IF Titer Assay</td>
<td>Negative</td>
</tr>
<tr>
<td>NMOFS</td>
<td>NMO/AQP4 FACS</td>
<td>Negative</td>
</tr>
<tr>
<td>NMOTS</td>
<td>NMO/AQP4 FACS Titer</td>
<td>Negative</td>
</tr>
<tr>
<td>WBN</td>
<td>Paraneoplastic Autoantibody WBlot</td>
<td>Negative</td>
</tr>
</tbody>
</table>
AGN1C  Anti-Glial Nuclear Ab, Type 1
ANN1C  Anti-Neuronal Nuclear Ab, Type 1
ANN2C  Anti-Neuronal Nuclear Ab, Type 2
ANN3C  Anti-Neuronal Nuclear Ab, Type 3
CS2CC  CASPR2-IgG CBA, CSF Negative
CRMWC  CRMP-5-IgG Western Blot, CSF Negative
CRMC  CRMP-5-IgG, CSF
DPPIC  DPPX Ab IFA, CSF Negative
GD65C  GAD65 Ab Assay, CSF
LG1CC  LGI1-IgG CBA, CSF Negative
GL1IC  mGluR1 Ab IFA, CSF Negative
NMDCC  NMDA-R Ab CBA, CSF Negative
PCTRC  Purkinje Cell Cytoplasmic Ab Type Tr
PCA1C  Purkinje Cell Cytoplasmic Ab Type 1
PCA2C  Purkinje Cell Cytoplasmic Ab Type 2
VGKCC  Neuronal (V-G) K+ Channel Ab, CSF

Test ID  Reporting Name  Reference Value

ABLTC  Amphiphysin Western Blot, CSF Negative
AMPIC  AMPA-R Ab IF Titer Assay, CSF
AMPCC  AMPA-R Ab CBA, CSF Negative
DPPTC  DPPX Ab IFA Titer, CSF
DPPCC  DPPX Ab CBA, CSF Negative
GABIC  GABA-B-R Ab IF Titer Assay, CSF
GABCC  GABA-B-R Ab CBA, CSF Negative
GL1TC  mGluR1 Ab IFA Titer, CSF
GL1CC  mGluR1 Ab CBA, CSF Negative
NMDIC  NMDA-R Ab IF Titer Assay, CSF
NMOFC  NMO/AQP4 FACS, CSF Negative
NMOCTC  NMO/AQP4 FACS Titer, CSF
WBNC  Paraneoplastic Autoantibody WBlot, CSF Negative


MPL Exon 10 Mutation Detection, Blood

Clinical Information: DNA sequence mutations in exon 10 of the myeloproliferative leukemia virus oncogene (MPL) have been detected in approximately 5% of patients with primary myelofibrosis (PMF) and essential thrombocythemia (ET), which are hematopoietic neoplasms classified within the broad category of myeloproliferative neoplasms. MPL codes for a transmembrane tyrosine kinase and the most common MPL mutations are single base-pair substitutions at codon 515. These mutations have
been shown to promote constitutive, cytokine-independent activation of the JAK/STAT signaling pathway, and contribute to the oncogenic phenotype. At least 8 different MPL exon 10 mutations have been identified in PMF and ET to date; mutations outside of exon 10 have not yet been reported. The vast majority of MPL mutations have been found in specimens testing negative for the most common mutation identified in myeloproliferative neoplasms, JAK2 V617F, although a small number of cases with both types of mutations have been reported. MPL mutations have not been identified in patients with polycythemia vera, chronic myelogenous leukemia, or other myeloid neoplasms. Identification of MPL mutations can aid in the diagnosis of a myeloproliferative neoplasm and is highly suggestive of either PMF or ET.

**Useful For:** Aiding in the distinction between a reactive cytosis and a myeloproliferative neoplasm in blood specimens

**Interpretation:** The results will be reported as 1 of 2 states: -Negative for MPL exon 10 mutation

-Positive for MPL exon 10 mutation If the result is positive, a description of the mutation at the nucleotide level and the altered protein sequence is reported. Positive mutation status is highly suggestive of a myeloproliferative neoplasm, but must be correlated with clinical and other laboratory features for a definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative or other neoplasm.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**MPL Exon 10 Mutation Detection, Reflex**

**Clinical Information:** The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR-ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide mutation in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). The JAK2 V617F is present in 95% to 98% of polycythemia vera (PV), and 50% to 60% of primary myelofibrosis (PMF) and essential thrombocythemia (ET). It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome. Detection of the JAK2 V617F is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate the absence of MPN. Other important molecular markers in BCR-ABL1-negative MPN include CALR exon 9 mutation (20%-30% of PMF and ET) and MPL exon 10 mutation (5%-10% of PMF and 3%-5% of ET). Mutations in JAK2, CALR, and MPL are essentially mutually exclusive. A CALR mutation is associated with decreased risk of thrombosis in both ET and PMF, and confers a favorable clinical outcome in PMF patients. A triple negative (JAK2 V617F, CALR, and MPL-negative) genotype is considered a high-risk molecular signature in PMF.

**Useful For:** Aiding in the distinction between a reactive cytosis and a chronic myeloproliferative disorder Evaluates for mutations in MPL in an algorithmic process for the MPNR / Myeloproliferative Neoplasm (MPN), JAK2 V617F with reflex to CALR and MPL.

**Interpretation:** An interpretation will be provided under the MPNR / Myeloproliferative Neoplasm (MPN), JAK2 V617F with reflex to CALR and MPL.

**Reference Values:**
Only orderable as a reflex. For more information see MPNR / Myeloproliferative Neoplasm (MPN), JAK2 V617F with reflex to CALR and MPL.

An interpretive report will be provided.

**MPL Exon 10 Mutation Detection, Varies**

**Clinical Information:** DNA sequence mutations in exon 10 of the myeloproliferative leukemia virus oncogene (MPL) have been detected in approximately 5% of patients with primary myelofibrosis (PMF) and essential thrombocythemia (ET), which are hematopoietic neoplasms classified within the broad category of myeloproliferative neoplasms. MPL codes for a transmembrane tyrosine kinase and the most common MPL mutations are single base pair substitutions at codon 515. These mutations have been shown to promote constitutive, cytokine-independent activation of the JAK/STAT signaling pathway and contribute to the oncogenic phenotype. At least 8 different MPL exon 10 mutations have been identified in PMF and ET to date, and mutations outside of exon 10 have not yet been reported. The vast majority of MPL mutations have been found in specimens testing negative for the most common mutation identified in myeloproliferative neoplasms, JAK2 V716F, although a small number of cases with both types of mutations have been reported. MPL mutations have not been identified in patients with polycythemia vera, chronic myelogenous leukemia, or other myeloid neoplasms. Identification of MPL mutations can aid in the diagnosis of a myeloproliferative neoplasm and is highly suggestive of either PMF or ET.

**Useful For:** Aiding in the distinction between a reactive cytosis and a myeloproliferative neoplasm
**Interpretation:** The results will be reported as 1 of 2 states: -Negative for MPL exon 10 mutation -Positive for MPL exon 10 mutation If the result is positive, a description of the mutation at the nucleotide level and the altered protein sequence is reported. Positive mutation status is highly suggestive of a myeloproliferative neoplasm, but must be correlated with clinical and other laboratory features for a definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative or other neoplasm.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**MPL-2, Immunostain (Bill Only)**

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 1548
**MSH6I**

**MSH-6, Immunostain (Bill Only)**

**Reference Values:**
This test is for billing purposes only.  
This is not an orderable test.

**MSH2Z**

**MSH2 Gene, Full Gene Analysis**

**Clinical Information:** Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC) is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3-prime end of the EPCAM gene have also been associated with Lynch syndrome, as this leads to inactivation of the MSH2 promoter. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer-associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome-related genes. The lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are <15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described but also include brain/central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of Lynch syndrome. One such strategy involves testing the tumors from suspected individuals for microsatellite instability (MSI) and immunohistochemistry (IHC) for the presence or absence of defective DNA mismatch repair. Tumors that demonstrate absence of expression of MSH2 and MSH6 are more likely to have a germline mutation in the MSH2 gene.

**Useful For:** Determining whether absence of MSH2 protein, by immunohistochemistry in tumor tissue, is associated with a germline mutation in the affected individual Establishing a diagnosis of Lynch syndrome/hereditary nonpolyposis colorectal cancer Identification of familial MSH2 mutation to allow for predictive testing in family members

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations,(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes: MLH1, MSH2, MSH6, and PMS2. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome-related genes and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include sebaceous neoplasms, gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are less than 15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described but also include brain and central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous or compound heterozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of Lynch syndrome. Testing tumors from individuals at risk for Lynch syndrome for microsatellite instability (MSI) indicates the presence or absence of defective DNA mismatch repair phenotype within the tumor, but does not suggest in which gene the abnormality rests. Tumors from individuals affected by Lynch syndrome usually demonstrate an MSI-H phenotype (MSI >30% of microsatellites examined). The MSI-H phenotype can also be seen in individuals whose tumors have somatic MLH1 promoter hypermethylation. Tumors from individuals that show the MSS/MSI-L phenotype (MSI <30% of microsatellites examined), are not likely to have Lynch syndrome or somatic hypermethylation of MLH1. Immunohistochemistry (IHC) is a complementary testing strategy to MSI testing. In addition to identifying tumors with defective DNA mismatch repair, IHC analysis is helpful for identifying the gene responsible for the defective DNA mismatch repair within the tumor, because the majority of MSI-H tumors show a loss of expression of at least 1 of the 4 mismatch repair genes described above. Testing is typically first performed on the tumor of an affected individual and in the context of other risk factors, such as young age at diagnosis or a strong family history of Lynch syndrome-related cancers. If defective DNA mismatch repair is identified within the tumor, mutation analysis of the associated gene can be performed to identify the causative germline mutation and allow for predictive testing of at-risk individuals. Of note, MSI-H phenotypes and loss of protein expression by IHC have also been demonstrated in various sporadic cancers, including those of the colon and endometrium. Absence of MLH1 and PMS2 protein expression within a tumor, for instance, is most often associated with a somatic alteration in individuals with an older age of onset of cancer than typical Lynch syndrome families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between somatic and germline mutations. Genetic testing of the gene indicated by IHC analysis can help to distinguish between these 2 possibilities. In addition, when absence of MLH1/PMS2 is observed, BRMLH / MLH1 Hypermethylation and BRAF Mutation Analyses, Tumor or ML1HM / MLH1 Hypermethylation Analysis, Tumor may also help to distinguish between a sporadic and germline etiology. It should be noted that this Lynch syndrome screen is not a genetic test, but rather stratifies the risk of having an inherited cancer predisposition syndrome, and identifies patients who might benefit from subsequent genetic testing.

Useful For: Evaluation of tumor tissue to identify patients at high risk for having hereditary
nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome Evaluation of tumor tissue to identify patients at risk for having hereditary endometrial carcinoma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**MSH6Z**

**MSH6 Gene, Full Gene Analysis**

**Clinical Information:** Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC) is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3-prime end of the EPCAM gene have also been associated with Lynch syndrome, as this leads to inactivation of the MSH2 promoter. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer-associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome-related genes. The lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are <15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described but also include brain/central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of Lynch syndrome. One such strategy involves testing the tumors from suspected individuals for microsatellite instability (MSI) and immunohistochemistry (IHC) for the presence or...
absence of defective DNA mismatch repair. Tumors that demonstrate absence of expression of MSH6 are more likely to have a germline mutation in the MSH6 gene.

**Useful For:** Determining whether absence of MSH6 protein, by immunohistochemistry in tumor tissue, is associated with a germline mutation in the affected individual. Establishing a diagnosis of Lynch syndrome/hereditary nonpolyposis colorectal cancer

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**MSH6 Immunostain, Technical Component Only**

**Clinical Information:** Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes: MLH1, MSH2, MSH6, and PMS2. HNPCC is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other HNPCC-related genes and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include sebaceous neoplasms, gastric cancer, ovarian cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are less than 15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the HNPCC spectrum. Several clinical variants of HNPCC have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations. Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described but also include brain and central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous or compound heterozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of HNPCC. Testing tumors from individuals at risk for HNPCC for microsatellite instability (MSI) indicates the presence or absence of defective DNA mismatch repair phenotype within the tumor, but does not suggest in which gene the abnormality rests. Tumors from individuals affected by HNPCC usually demonstrate an MSI-H phenotype (MSI >30% of microsatellites examined). The MSI-H phenotype can also be seen in individuals whose tumors have somatic MLH1 promoter hypermethylation. Tumors from individuals that show the MSS/MSI-L phenotype (MSI at <30% of microsatellites examined), are not likely to have HNPCC or somatic hypermethylation of MLH1. Immunohistochemistry (IHC) is a complementary testing strategy to MSI testing. In addition to identifying tumors with defective DNA mismatch repair, IHC analysis is helpful for identifying the gene responsible for the defective DNA mismatch repair within the tumor, because the majority of MSI-H tumors show a loss of expression of at least 1 of the 4 mismatch
repair genes described above. Testing is typically first performed on the tumor of an affected individual and in the context of other risk factors, such as young age at diagnosis or a strong family history of HNPCC-related cancers. If defective DNA mismatch repair is identified within the tumor, mutation analysis of the associated gene can be performed to identify the causative germline mutation and allow for predictive testing of at-risk individuals. Of note, MSI-H phenotypes and loss of protein expression by IHC have also been demonstrated in various sporadic cancers, including those of the colon and endometrium. Absence of MLH1 and PMS2 protein expression within a tumor, for instance, is most often associated with a somatic alteration in individuals with an older age of onset of cancer than typical HNPCC families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between somatic and germline mutations. Genetic testing of the gene indicated by IHC analysis can help to distinguish between these 2 possibilities. In addition, when absence of MLH1/PMS2 is observed, BRMLH / MLH1 Hypermethylation and BRAF Mutation Analyses, Tumor or ML1HM / MLH1 Hypermethylation Analysis, Tumor may also help to distinguish between a sporadic and germline etiology. It should be noted that this HNPCC screen is not a genetic test, but rather stratifies the risk of having an inherited cancer predisposition syndrome, and identifies patients who might benefit from subsequent genetic testing.

**Useful For:** Evaluation of tumor tissue to identify patients at high risk for having hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome Evaluation of tumor tissue to identify patients at risk for having hereditary endometrial carcinoma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**MPCPD 64968**
**mSMART, Plasma Cell Proliferative Disorder (PCPD), FISH**

**Reference Values:**
Only orderable as part of a profile. For more information see MSMRT / Mayo Algorithmic Approach for Stratification of Myeloma and Risk-Adapted Therapy Report.

**MTBVP 60270**
**Mt PZA Confirmation, pncA Sequencing (Bill Only)**

**Reference Values:**
MUCN4
601740
Mucin 4, Immunostain, Technical Component Only

Clinical Information: Mucin 4 (MUC4) is a large membrane-anchored glycoprotein that belongs to the mucin family. Mucins play important roles in the protection of epithelial cells and have been implicated in epithelial renewal and differentiation. MUC4 is expressed in the cytoplasm and membrane of respiratory, gastrointestinal, cervical, and prostatic epithelial cells. Overexpression of MUC4 has been observed in many carcinomas. It has been shown to be useful for the distinction between sarcomatoid carcinoma (often expressed) versus sarcomatoid mesothelioma (usually negative).

Useful For: Aids in the differentiation of sarcomatoid carcinoma from sarcomatoid mesothelioma

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist is required order PATHC / Pathology Consultation. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


MCIVP
35482
Mucolipidosis IV, Mutation Analysis, IVS3(-2)A->G and del6.4kb

Clinical Information: Mucolipidosis IV is a lysosomal storage disease characterized by mental retardation, hypotonia, corneal clouding, and retinal degeneration. Mutations in the MCOLN1 gene are responsible for the clinical manifestations of mucolipidosis IV. The carrier rate in the Ashkenazi Jewish population is 1 in 127. Two mutations in the MCOLN1 gene account for the majority of mutations in the Ashkenazi Jewish population: IVS3(-2)A->G and del6.4kb. The detection rate for these 2 mutations is approximately 95%.

Useful For: Carrier testing for mucolipidosis IV in individuals of Ashkenazi Jewish ancestry Prenatal diagnosis of mucolipidosis IV for at-risk pregnancies Confirmation of suspected clinical diagnosis of mucolipidosis IV in individuals of Ashkenazi Jewish ancestry

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.


MQLNR
38000
Mucopolysaccharides (MPS) Qualitative, Urine

Clinical Information: The mucopolysaccharidoses (MPS) are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan...
sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAG, also called mucopolysaccharides). Undegraded or partially degraded GAG are stored in lysosomes and excreted in the urine. Accumulation of GAG in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in MPS disorders. There are 11 known enzyme deficiencies that result in MPS. In addition, abnormal GAG storage is observed in multiple sulfatase deficiency and in I-cell disease. Finally, an abnormal excretion of GAG in urine is observed occasionally in other disorders including active bone diseases, connective tissue disease, hypothyroidism, urinary dysfunction, and oligosaccharidoses. Using liquid chromatography-tandem mass spectrometry, this qualitative urine MPS screen provides analysis of the specific sulfates that are associated with at least 13 different diseases.

**Useful For:** Screening for mucopolysaccharidoses (MPS)

**Interpretation:** The pattern of sulfates obtained by liquid chromatography-tandem mass spectrometry is usually characteristic of the enzyme deficiency. When abnormal results are detected with characteristic patterns, a detailed interpretation is given, including an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro confirmatory studies (enzyme assay and molecular test).

**Reference Values:**
Only orderable as part of a profile. See LYSDU / Lysosomal Storage Disorders Screen, Urine.

For information regarding qualitative mucopolysaccharides, see MPSSC / Mucopolysaccharides (MPS) Screen, Urine.


**MPSSC**

**Mucopolysaccharides (MPS) Screen, Urine**

**Clinical Information:** The mucopolysaccharidoses (MPSs) are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAGs). Undegraded or partially degraded GAGs (also called mucopolysaccharides) are stored in lysosomes and excreted in the urine. Accumulation of GAGs in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in MPS disorders. There are 11 known enzyme deficiencies that result in MPS. In addition, abnormal GAG storage is observed in multiple sulfatase deficiency and in I-cell disease. Finally, an abnormal excretion of GAGs in urine is observed occasionally in other disorders including active bone diseases, connective tissue disease, hypothyroidism, urinary dysfunction, and oligosaccharidoses. MPS are autosomal recessive disorders with the exception of MPS II, which follows an X-linked inheritance pattern. Affected individuals typically experience a period of normal growth and development followed by progressive disease involvement encompassing multiple systems. The severity and features vary and may include facial coarsening, organomegaly, skeletal changes, cardiac abnormalities, and developmental delays. Moreover, disease presentation varies from as early as late infancy to adulthood. A diagnostic workup for individuals with suspected MPS should begin with MPSSC / Mucopolysaccharides (MPS) Screen, Urine, which includes both the quantitative analysis of total GAGs and qualitative liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis of the specific sulfates. Interpretation is based upon pattern recognition of the specific sulfates detected by MS/MS and the qualitative analysis of their relative amounts of excretion. However, an abnormal MPS analysis is not sufficient to conclusively establish a specific diagnosis. It is strongly recommended to seek confirmation by an independent method, typically in vitro enzyme assay (available in either blood or cultured fibroblasts from a skin biopsy) and/or molecular analysis. After a specific diagnosis has been established, MPSQN / Mucopolysaccharides (MPS), Quantitative, Urine, which does not include the analysis of the specific sulfates, can be appropriate for monitoring the effectiveness of treatment, such as a bone marrow transplant or enzyme replacement therapy. However,
some clinicians will opt to perform the MPS screen, which allows for monitoring of not only the total amount of GAGs, but also the excretion of specific sulfates, as these may change in patients with an MPS disorder undergoing treatment. Table: Enzyme Defects and Excretion Products of Mucopolysaccharidoses Disorder Alias Enzyme Deficiency (Mayo Medical Laboratories’ Test, if applicable) Sulfates Excreted MPS I Hurler/Scheie alpha-L-iduronidase (IDSWB, IDSBS) DS/HS MPS II Hunter Iduronate 2-sulfatase (12SW, 12BSB) DS/HS MPS III A Sanfilippo A Heparan N-sulfatase HS MPS III B Sanfilippo B N-acetyl-alpha-D-glucosaminidase (ANAS) HS MPS III C Sanfilippo C Acetyl-CoA:alpha-glucosaminide N-acetylttransferase HS MPS III D Sanfilippo D N-acetylglucosamine-6-sulfatase HS MPS IV A Morquio A Galactosamine-6-sulfatase (G6ST) KS/C6S MPS IV B Morquio B beta-galactosidase (BGA, BGAW, BGABS) KS MPS VI Maroteaux-Lamy Arylsulfatase B (ARSB) DS MPS IX Hyaluronidase deficiency Hyaluronidase None KEY: C6S, chondroitin 6-sulfate; DS, derminate sulfate; HS, heparan sulfate; KS, keratan sulfate MPS I (Hunter/Scheie syndrome) is caused by a reduced or absent activity of the alpha-L-iduronidase enzyme. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. This enzyme deficiency results in a wide range of clinical phenotypes that are further categorized into 3 main types: MPS IH (Hunter syndrome), MPS IS (Scheie syndrome), and MPS IH/S (Hurler-Scheie syndrome), which are not distinguishable via biochemical methods. Clinically, they are also referred to as MPS I and attenuated MPS I. MPS IH is the most severe and has an early onset consisting of skeletal deformities, coarse facial features, hepatosplenomegaly, macrocephaly, cardiomyopathy, hearing loss, macroglossia, and respiratory tract infections. Developmental delay is noticed as early as 12 months with death occurring usually before 10 years of age. MPS IH/S has an intermediate clinical presentation characterized by progressive skeletal symptoms called dysostosis multiplex. Individuals typically have little or no intellectual dysfunction. Corneal clouding, joint stiffness, deafness, and valvular heart disease can develop by early to mid-teens. Survival into adulthood is common. Cause of death usually results from cardiac complications or upper airway obstruction. Comparatively, MPS IS presents with the mildest phenotype. The onset occurs after 5 years of age. It is characterized by normal intelligence and stature; however, affected individuals do experience joint involvement, visual impairment, and obstructive airway disease. MPS II (Hunter syndrome) is caused by a reduced or absent activity of the enzyme iduronate 2-sulfatase. The clinical features and severity of symptoms of MPS II are widely variable ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. The clinical presentation of MPS II is similar to that of MPS I with the notable difference of the lack of corneal clouding in MPS II. The inheritance pattern is X-linked and as such MPS II is observed almost exclusively in males with an estimated incidence of 1 in 170,000 male births. Symptomatic carrier females have been reported, but are very rare. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS III (Sanfilippo syndrome) is caused by a reduced or absent activity of 1 of 4 enzymes (see Table above), resulting in a defect of heparan sulfate degradation. Patients with MPS III uniformly excrete heparan sulfate resulting in similar clinical phenotypes, and are further classified as type A, B, C, or D based upon the specific enzyme deficiency. Sanfilippo syndrome is characterized by severe central nervous system (CNS) degeneration, but only mild physical disease. Such disproportionate involvement of the CNS is unique among the MPS. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the 20s. The occurrence of MPS III varies by subtype with types A and B being the most common and types C and D being very rare. The collective incidence is approximately 1 in 58,000 live births. MPS IVA (Morquio A syndrome) is caused by a reduced or absent N-acetylgalactosamine-6-sulfate sulfatase. Clinical features and severity of symptoms of MPS IVA are widely variable, but may include skeletal dysplasia, short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Estimates of the incidence of MPS IVA syndrome range from 1 in 200,000 to 1 in 300,000 live births. Treatment with enzyme replacement therapy is available. MPS IVB (Morquio B syndrome) is caused by a reduced or absent beta-galactosidase activity, which gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms of MPS IVB are widely variable ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general,
symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. The incidence of MPS IVB is estimated to be about 1 in 250,000 live births. Treatment options are limited to symptomatic management. MPS VI (Maroteaux-Lamy syndrome) is caused by a deficiency of the enzyme arylsulfatase B. Clinical features and severity of symptoms are widely variable, but typically include short stature, dysostosis multiplex, facial dysmorphism, stiff joints, claw-hand deformities, carpal tunnel syndrome, hepatosplenomegaly, corneal clouding, and cardiac defects. Intelligence is usually normal. Estimates of the incidence of MPS VI range from 1 in 200,000 to 1 in 300,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS VII (Sly syndrome) is caused by a deficiency of the enzyme beta-glucuronidase. The phenotype varies significantly from mild to severe presentations and may include macrocephaly, short stature, dysostosis multiplex, hepatomegaly, coarse facies, and impairment of cognitive function. Likewise, the age of onset is variable ranging from prenatal to adulthood. MPS VII is extremely rare, affecting approximately 1 in 1,500,000 individuals. MPS IX is a very rare disorder caused by a deficiency of the enzyme hyaluronidase. Patients present with short stature, flat nasal bridge, and joint findings. Urine GAGs are normal in MPS IX. Multiple sulfatase deficiency (MSD) is an autosomal recessive disorder caused by mutations in the sulfatase-modifying factor-1 gene (SUMF1). Sulfatases undergo a common process that allows for normal expression of enzyme activity. Mutations in SUMF1 impair that process, thereby resulting in decreased activity of all known sulfatase enzymes. Individuals with MSD have a complex clinical presentation encompassing features of each of the distinct enzyme deficiencies, including iduronate 2-sulfatase (MPS II), N-acetylgalactosamine-6-sulfate sulfatase (MPS IVA), arylsulfatase B (MPS VI), and arylsulfatase A (metachromatic leukodystrophy), steroid sulfatase (X-linked ichthyosis) and arylsulfatase E (chondrodysplasia punctata). MSD is extremely rare, affecting approximately 1 in 1,400,000 individuals.

Useful For: Preferred screening test for mucopolysaccharidoses

Interpretation: An abnormally elevated excretion of glycosaminoglycans is characteristic of mucopolysaccharidoses. The pattern of sulfates obtained by liquid chromatography-tandem mass spectrometry (LC-MS/MS) is usually characteristic of the enzyme deficiency. When abnormal results are detected with characteristic patterns, a detailed interpretation is given, including an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro confirmatory studies (enzyme assay and molecular test).

Reference Values:
MPS, QUANTITATIVE
0-4 months: < or =53.0 mg/mmol creatinine
5-18 months: < or =31.0 mg/mmol creatinine
19 months-2 years: < or =24.0 mg/mmol creatinine
3-5 years: < or =16.0 mg/mmol creatinine
6-10 years: < or =12.0 mg/mmol creatinine
11-14 years: < or =10.0 mg/mmol creatinine
>14 years: < or =6.5 mg/mmol creatinine

MPS, QUALITATIVE
An interpretive report will be provided.


MPSQN 81473
Mucopolysaccharides (MPS), Quantitative, Urine

Clinical Information: The mucopolysaccharidoses (MPS) are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan
sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans; GAGs). Undegraded or partially degraded GAGs (also called mucopolysaccharides) are stored in lysosomes and excreted in the urine. Accumulation of GAGs in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in MPS disorders. There are 11 known enzyme deficiencies that result in MPS. In addition, abnormal GAG storage is observed in multiple sulfatase deficiency and in I-cell disease. Finally, an abnormal excretion of GAGs in urine is observed occasionally in other disorders including active bone diseases, connective tissue disease, hypothyroidism, urinary dysfunction, and oligosaccharidoses. MPS are autosomal recessive disorders with the exception of MPS II, which follows an X-linked inheritance pattern. Affected individuals typically experience a period of normal growth and development followed by progressive disease involvement encompassing multiple systems. The severity and features vary, and may include facial coarsening, organomegaly, skeletal changes, cardiac abnormalities, and developmental delays. Moreover, disease presentation varies from as early as late infancy to adulthood. A diagnostic workup for individuals with suspected MPS should begin with MPSSC / Mucopolysaccharides (MPS) Screen, Urine, which includes both the quantitative analysis of total GAGs and qualitative liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis of the specific sulfates. Interpretation is based upon pattern recognition of the specific sulfates detected by MS/MS and the qualitative analysis of their relative amounts of excretion. However, an abnormal MPS analysis is not sufficient to conclusively establish a specific diagnosis. It is strongly recommended to seek confirmation by an independent method, typically in vitro enzyme assay (available in either blood or cultured fibroblasts from a skin biopsy) or molecular analysis. After a specific diagnosis has been established, MPSQN / Mucopolysaccharides (MPS), Quantitative, Urine, which does not include the analysis of the specific sulfates, can be appropriate for monitoring the effectiveness of treatment, such as a bone marrow transplant or enzyme replacement therapy. However, some clinicians will opt to perform the MPS screen, which allows for monitoring of not only the total amount of GAGs, but also the excretion of specific sulfates, as these may change in patients with an MPS disorder undergoing treatment. Table: Enzyme Defects and Excretion Products of Mucopolysaccharidoses Disorder Alias Enzyme Deficiency (Mayo Medical Laboratories’ Test, if applicable) Sulfate(s) Excreted MPS I Hunter/Scheie alpha-L-iduronidase (IDSWB, IDSBS) DS/HS MPS II Hunter Iduorate 2-sulfatase (12SW, 12BS) DS/HS MPS III A Sanfilippo A Heparan N-sulfatase HS MPS III B Sanfilippo B N-acetyl-alpha-D-glucosaminidase (ANAS) HS MPS III C Sanfilippo C Acetyl-CoA:alpha-glucosaminide N-acetyltransferase HS MPS III D Sanfilippo D N-acetylglucosamine-6-sulfatase HS MPS IV A Morquio A Galactosamine-6-sulfatase (G6ST) KS/C6S MPS IV B Morquio B beta-galactosidase (BGA, BGAW, BGABS) KS MPS VI Maroteaux-Lamy Arylsulfatase B (ARSB) DS MPS IX Hyaluronidase deficiency Hyaluronidase None C6S, chondroitin 6-sulfate; DS, dermatan sulfate; HS, heparan sulfate; KS, keratan sulfate MPS I (Hurler/Scheie syndrome) is caused by a reduced or absent activity of the alpha-L-iduronidase enzyme. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. This enzyme deficiency results in a wide range of clinical phenotypes that are further categorized into 3 main types: MPS IH (Hurler syndrome), MPS IS (Scheie syndrome), and MPS IH/S (Hurler-Scheie syndrome), which are not distinguishable via biochemical methods. Clinically, they are also referred to as MPS I and attenuated MPS I. MPS IH is the most severe and has an early onset consisting of skeletal deformities, coarse facial features, hepatosplenomegaly, macrocephaly, cardiomyopathy, hearing loss, macroglossia, and respiratory tract infections. Developmental delay is noticed as early as 12 months with death occurring usually before 10 years of age. MPS IH/S has an intermediate clinical presentation characterized by progressive skeletal symptoms called dysostosis multiplex. Individuals typically have little or no intellectual dysfunction. Corneal clouding, joint stiffness, deafness, and valvular heart disease can develop by early to mid-teens. Survival into adulthood is common. Cause of death usually results from cardiac complications or upper airway obstruction. Comparatively, MPS IS presents with the mildest phenotype. The onset occurs after 5 years of age. It is characterized by normal intelligence and stature; however, affected individuals do experience joint involvement, visual impairment, and obstructive airway disease. MPS II (Hunter syndrome) is caused by a reduced or absent activity of the enzyme iduronate 2-sulfatase. The clinical features and severity of symptoms of MPS II are widely variable ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. The clinical presentation of MPS II is similar to that of MPS I with the notable difference of the lack of corneal clouding in MPS II. The inheritance pattern is X-linked and as such MPS II is observed almost
exclusively in males with an estimated incidence of 1 in 170,000 male births. Symptomatic carrier females have been reported, but are very rare. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS III (Sanfilippo syndrome) is caused by a reduced or absent activity of any 1 of 4 enzymes (see Table above), resulting in a defect of heparan sulfate degradation. Patients with MPS III uniformly excrete heparan sulfate resulting in similar clinical phenotypes, and are further classified as type A, B, C, or D based upon the specific enzyme deficiency. Sanfilippo syndrome is characterized by severe central nervous system (CNS) degeneration, but only mild physical disease. Such disproportionate involvement of the CNS is unique among the MPSs. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the 20s. The occurrence of MPS III varies by subtype with types A and B being the most common and types C and D being very rare. The collective incidence is approximately 1 in 58,000 live births. MPS IVA (Morquio A syndrome) is caused by a reduced or absent N-acetylgalactosamine-6-sulfate sulfatase. Clinical features and severity of symptoms of MPS IVA are widely variable, but may include skeletal dysplasia, short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Estimates of the incidence of MPS IVA syndrome range from 1 in 200,000 to 1 in 300,000 live births. Treatment with enzyme replacement therapy is available. MPS IVB (Morquio B syndrome) is caused by a reduced or absent beta-galactosidase activity, which gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms of MPS IVB are widely variable ranging from severe disease to an attenuated form which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. The incidence of MPS IVB is estimated to be about 1 in 250,000 live births. Treatment options are limited to symptomatic management. MPS VI (Maroteaux-Lamy syndrome) is caused by a deficiency of the enzyme arylsulfatase B. Clinical features and severity of symptoms are widely variable, but typically include short stature, dysostosis multiplex, facial dysmorphism, stiff joints, claw-hand deformities, carpal tunnel syndrome, hepatosplenomegaly, corneal clouding, and cardiac defects. Intelligence is usually normal. Estimates of the incidence of MPS VI range from 1 in 200,000 to 1 in 300,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS VII (Sly syndrome) is caused by a deficiency of the enzyme beta-glucuronidase. The phenotype varies significantly from mild to severe presentations and may include macrocephaly, short stature, dysostosis multiplex, hepatomegaly, coarse facies, and impairment of cognitive function. Likewise, the age of onset is variable ranging from prenatal to adulthood. MPS VII is extremely rare, affecting approximately 1 in 1,500,000 individuals. MPS IX is a very rare disorder caused by a deficiency of the enzyme hyaluronidase. Patients present with short stature, flat nasal bridge, and joint findings. Urine GAGs are normal in MPS IX. Multiple sulfatase deficiency (MSD) is an autosomal recessive disorder caused by mutations in the sulfatase-modifying factor-1 gene (SUMF1). Sulfatases undergo a common process that allows for normal expression of enzyme activity. Mutations in SUMF1 impair that process, thereby resulting in decreased activity of all known sulfatase enzymes. Individuals with MSD have a complex clinical presentation encompassing features of each of the distinct enzyme deficiencies, including iduronate 2-sulfatase (MPS II), N-acetylgalactosamine-6-sulfate sulfatase (MPS IVA), arylsulfatase B (MPS VI), arylsulfatase A (metachromatic leukodystrophy), steroid sulfatase (X-linked ichthyosis) and arylsulfatase E (chondrodysplasia punctata). MSD is extremely rare, affecting approximately 1 in 1,400,000 individuals. The preferred test to screen for mucopolysaccharidoses (MPS) is MPSFC / Mucopolysaccharides (MPS) Screen, Urine, which includes both the quantitative analysis of total glycosaminoglycans and qualitative liquid chromatography-tandem mass spectrometry analysis of the specific sulfates.

**Useful For:** Monitoring patients with mucopolysaccharidosis who have had bone marrow transplants or are receiving enzyme therapy

**Interpretation:** An abnormally elevated excretion of glycosaminoglycan (GAG) is characteristic of mucopolysaccharidoses. GAG levels may normalize or remain elevated in patients who have undergone bone marrow transplants or are receiving enzyme replacement therapy.

**Reference Values:**

0-4 months: < or =53.0 mg/mmol creatinine
5-18 months: < or =31.0 mg/mmol creatinine
19 months-2 years: < or =24.0 mg/mmol creatinine
3-5 years: < or =16.0 mg/mmol creatinine
6-10 years: < or =12.0 mg/mmol creatinine
11-14 years: < or =10.0 mg/mmol creatinine
>14 years: < or =6.5 mg/mmol creatinine


Mucopolysaccharides (MPS), Quantitative, Urine

Clinical Information: The mucopolysaccharidoses (MPS) are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans; GAGs, also called mucopolysaccharides). Undegraded or partially degraded GAGs (also called mucopolysaccharides) are stored in lysosomes and excreted in the urine. Accumulation of GAGs in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in MPS disorders. There are 11 known enzyme deficiencies that result in MPS. In addition, abnormal GAG storage is observed in multiple sulfatase deficiency and in I-cell disease. Finally, an abnormal excretion of GAGs in urine is observed occasionally in other disorders including active bone diseases, connective tissue disease, hypothyroidism, urinary dysfunction, and oligosaccharidoses. For information regarding quantitative mucopolysaccharides, see MPSQN / Mucopolysaccharides (MPS), Quantitative, Urine.

Useful For: Monitoring patients with mucopolysaccharidosis who have had bone marrow transplants or are receiving enzyme therapy

Interpretation: An abnormally elevated excretion of glycosaminoglycan (GAG) is characteristic of mucopolysaccharidoses. GAG levels may normalize or remain elevated in patients who have undergone bone marrow transplants or are receiving enzyme replacement therapy.

Reference Values:
Only orderable as part of a profile. See LYSDU / Lysosomal Storage Disorders Screen, Urine.

For information regarding quantitative mucopolysaccharides, see MPSQN / Mucopolysaccharides (MPS), Quantitative, Urine.


Mucopolysaccharidosis III, Multi-Gene Panel

Clinical Information: Mucopolysaccharidosis type III (MPS-III), also known as Sanfilippo syndrome, is an autosomal recessive condition that consists of 4 different types (A, B, C, and D). Each type of MPS-III results from the absence of 1 of 4 lysosomal enzymes, which leads to the accumulation of heparan sulfate in various tissues. Sanfilippo syndrome A is caused by mutations in SGSH and is characterized by reduced or absent activity of the sulfamidase enzyme. Sanfilippo syndrome B is caused by mutations in NAGLU and is characterized by reduced or absent activity of the N-acetyl-alpha-D-glucosaminidase. Sanfilippo syndrome C is caused by mutations in HGSNAT and is characterized by reduced or absent activity of the acetyl-CoA:alpha-glucosaminide N-acetyltransferase enzyme. Sanfilippo syndrome D is caused by mutations in GNS and is characterized by reduced or absent activity of the N-acetylglucosamine-6-sulfatase enzyme. Sanfilippo syndrome presents with a spectrum of
Sanfilippo syndrome is characterized by severe central nervous system degeneration with only mild physical disease. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years, accompanied by a rapid deterioration of social and adaptive skills.

**Useful For:** Identifying mutations within the SGSH, NAGLU, HGSNAT, and GNS genes

**Confirmation of a diagnosis of mucopolysaccharidosis type III, also known as Sanfilippo syndrome**

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

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**MP3AZ 35502**

**Mucopolysaccharidosis IIIA, Full Gene Analysis**

**Clinical Information:** Mucopolysaccharidosis type III (MPS-III), also known as Sanfilippo syndrome, is an autosomal recessive condition that consists of 4 different types (A, B, C, and D). Each type of MPS-III results from the absence of 1 of 4 lysosomal enzymes, which leads to the lysosomal accumulation of heparan sulfatase. Mucopolysaccharidosis type IIIA (MPS-IIIA), or Sanfilippo syndrome A, is caused by mutations in the SGSH gene and is characterized by reduced or absent activity of the sulfamidase enzyme. This test screens for mutations in all 8 exons of the SGSH gene. Sanfilippo syndrome is characterized by severe central nervous system degeneration with only mild physical disease. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the 20s.

**Useful For:** Identifying mutations within the SGSH gene Confirmation of a diagnosis of mucopolysaccharidosis type IIIA Carrier testing, when there is a family history of mucopolysaccharidosis type IIIA, but disease-causing mutations have not been previously identified

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**
Mucopolysaccharidosis IIIB, Full Gene Analysis

Clinical Information: Mucopolysaccharidosis type III (MPS-III), also known as Sanfilippo syndrome, is an autosomal recessive condition that consists of 4 different types (A, B, C, and D). Each type of MPS-III results from the absence of 1 of 4 lysosomal enzymes, which leads to the lysosomal accumulation of heparan sulfate. Mucopolysaccharidosis type IIIB (MPS-IIIB), or Sanfilippo syndrome B, is caused by mutations in the NAGLU gene and is characterized by reduced or absent activity of the N-acetyl-alpha-D-glucosaminidase. This test screens for mutations in all 6 exons of the NAGLU gene. Sanfilippo syndrome is characterized by severe central nervous system degeneration with only mild physical disease. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the 20s.

Useful For: Identifying mutations within the NAGLU gene Confirmation of a diagnosis of mucopolysaccharidosis type IIIB Carrier testing, when there is a family history of mucopolysaccharidosis type IIIB, but disease-causing mutations have not been previously identified

Interpretation: All detected alterations will be evaluated according to American College of Medical Genetics and Genomics recommendations. Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


Mucopolysaccharidosis IIIC, Full Gene Analysis

Clinical Information: Mucopolysaccharidosis type III (MPS-III), also known as Sanfilippo syndrome, is an autosomal recessive condition that consists of 4 different types (A, B, C, and D). Each type of MPS-III results from the absence of 1 of 4 lysosomal enzymes, which leads to the lysosomal accumulation of heparan sulfate. Mucopolysaccharidosis type IIIC (MPS-IIIC), or Sanfilippo syndrome C, is caused by mutations in the HGSNAT gene and is characterized by reduced or absent activity of the heparin acetyl-CoA:alpha-glucosaminide N-acetyltransferase enzyme. This test screens for mutations in all 18 exons of the HGSNAT gene. Sanfilippo syndrome is characterized by severe central nervous system (CNS) degeneration with only mild physical disease. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the 20s.

Useful For: Identifying mutations within the HGSNAT gene Confirmation of a diagnosis of mucopolysaccharidosis type IIIC Carrier testing, when there is a family history of mucopolysaccharidosis type IIIC, but disease-causing mutations have not been previously identified

Interpretation: All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.

Mucopolysaccharidosis IIID, Full Gene Analysis

Clinical Information: Mucopolysaccharidosis type III (MPS-III), also known as Sanfilippo syndrome, is an autosomal recessive condition that consists of 4 different types (A, B, C, and D). Each type of MPS-III results from the absence of 1 of 4 lysosomal enzymes, which leads to the lysosomal accumulation of heparan sulfate. Mucopolysaccharidosis type IIID (MPS-IIID), or Sanfilippo syndrome D, is caused by mutations in the GNS gene and is characterized by reduced or absent activity of the N-acetylglucosamine-6-sulfatase enzyme. This test screens for mutations in all 14 exons of the GNS gene. Sanfilippo syndrome is characterized by severe central nervous system (CNS) degeneration with only mild physical disease. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the 20s.

Useful For: Identifying mutations within the GNS gene Confirmation of a diagnosis of mucopolysaccharidosis type IIID Carrier testing when there is a family history of mucopolysaccharidosis type IIID, but disease-causing mutations have not been previously identified

Interpretation: All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. (1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.


Mucopolysaccharidosis VI, Full Gene Analysis

Clinical Information: Mucopolysaccharidosis type VI (MPS-VI), also known as Maroteaux-Lamy syndrome, is an autosomal recessive condition that consists of 4 different types (A, B, C, and D). Each type of MPS-VI results from the absence of 1 of 4 lysosomal enzymes, which leads to the lysosomal accumulation of heparan sulfate. Mucopolysaccharidosis type IIID (MPS-IIID), or Sanfilippo syndrome D, is caused by mutations in the GNS gene and is characterized by reduced or absent activity of the N-acetylglucosamine-6-sulfatase enzyme. This test screens for mutations in all 8 exons of the ARSB gene. The clinical features and severity of symptoms of Maroteaux-Lamy are widely variable. Typically it is characterized by short stature, dysostosis multiplex, facial dysmorphism, stiff joints, hepatosplenomegaly, corneal clouding, cardiac defects, and usually normal intelligence. With a rapidly progressing form of MPS-VI, onset occurs before 2 to 3 years of age with death typically occurring in the second to third decade. With a slowly progressing form of MPS-VI, a diagnosis usually occurs after 5 years of age but may not occur until the second or third decade. The recommended first-tier test for MPS-VI is biochemical testing that measures arylsulfatase B enzyme activity in fibroblasts (ARSB / Arylsulfatase B, Fibroblasts). Individuals with decreased or absent enzyme activity are more likely to have 2 identifiable mutations in the ARSB gene by molecular genetic testing. However, enzymatic testing is not reliable to detect carriers.

Useful For: Identifying mutations within the ARSB gene Confirmation of a diagnosis of mucopolysaccharidosis type VI Carrier testing, when there is a family history of mucopolysaccharidosis type VI, but disease-causing mutations have not been previously identified

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

MPSWB
Mucopolysaccharidosis, Blood

Clinical Information: The mucopolysaccharidoses (MPS) are a group of disorders caused by a deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAGs, also called mucopolysaccharides). Undegraded or partially degraded GAGs are stored in lysosomes and excreted in the urine. Accumulation of GAGs in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in MPS disorders. Depending on the extent of the enzyme deficiency and type of accumulating storage material, MPS patients may present with a variety of clinical findings that can include coarse facial features, cardiac abnormalities, organomegaly, intellectual disabilities, short stature and skeletal abnormalities. MPS I is an autosomal recessive disorder caused by reduced or absent activity of the enzyme alpha-L-iduronidase due to mutations in the IDUA gene. This enzyme deficiency results in a wide range of clinical phenotypes that are further categorized as MPS IH (Hurler syndrome), MPS IS (Scheie syndrome), and MPS IH/S (Hurler-Scheie syndrome), and which cannot be distinguished via biochemical methods. Clinically, they are also referred to as MPS I and attenuated MPS I. MPS IH is the most severe and has an early onset consisting of skeletal deformities, coarse facial features, hepatosplenomegaly, macrocephaly, cardiomyopathy, hearing loss, macroglossia, and respiratory tract infections. Developmental delay is noticed as early as 12 months, and without treatment, death usually occurs before 10 years of age. MPS IH/S has an intermediate clinical presentation characterized by progressive skeletal symptoms called dysostosis multiplex. Individuals typically have little or no intellectual dysfunction. Corneal clouding, joint stiffness, deafness, and valvular heart disease can develop by early to mid-teens. Survival into adulthood is common. Comparatively, MPS IS presents with the mildest phenotype. The onset occurs after 5 years of age. It is characterized by normal intelligence and stature; however, affected individuals do experience joint involvement, visual impairment, and obstructive airway disease. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS II, Hunter syndrome is an X-linked lysosomal storage disorder caused by a reduced or absent activity of the enzyme iduronate 2-sulfatase. The clinical features and severity of symptoms of MPS II are widely variable ranging from severe disease to an attenuated form, which generally presents later in life with a milder clinical presentation. In general, symptoms may include coarse facial features, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. The clinical presentation of MPS II is similar to that of MPS I with the notable difference of the lack of corneal clouding in MPS II. Due to the x-linked inheritance pattern, MPS II is observed almost exclusively in males with an estimated incidence of 1 in 170,000 male births. Symptomatic carrier females have been reported, but are very rare. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy MPS-III, Sanfilippo syndrome is caused by a reduced or absent activity of 1 of 4 enzymes involved in heparan sulfate degradation. Patients with MPS III uniformly excrete heparan sulfate resulting in similar clinical
phenotypes, and are further classified as type A, B, C, or D based upon the specific enzyme deficiency.

Sanfilippo syndrome is characterized by severe central nervous system (CNS) degeneration, but only mild physical disease. Such disproportionate involvement of the CNS is unique among the MPSs. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the 20s. The occurrence of MPS III varies by subtype with types A and B being the most common and types C and D being very rare. The collective incidence is approximately 1 in 58,000 live births. MPS IVA, Morquio A syndrome is caused by a reduced or absent N-acetylgalactosamine-6-sulfate sulfatase. Clinical features and severity of symptoms of MPS IVA are widely variable, but may include skeletal dysplasia, short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Estimates of the incidence of MPS IVA syndrome range from 1 in 200,000 to 1 in 300,000 live births. Treatment with enzyme replacement therapy is available. MPS IVB, Morquio B syndrome is caused by a reduced or absent beta-galactosidase activity, which gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms of MPS IVB are widely variable ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. The incidence of MPS IVB is estimated to be about 1 in 250,000 live births. Treatment options are limited to symptomatic management. MPS VI; Maroteaux-Lamy syndrome is an autosomal recessive lysosomal storage disorder caused by the deficiency of the enzyme arylsulfatase B. Clinical features and severity of symptoms are widely variable, but typically include short stature, dysostosis multiplex, facial dysmorphism, stiff joints, claw-hand deformities, carpal tunnel syndrome, hepatosplenomegaly, corneal clouding, and cardiac defects. Intelligence is usually normal. Rapidly progressing forms have an early onset of symptoms, significantly elevated GAGs especially dermatan sulfate, and can lead to death before the second or third decade. A more slowly progressing form has a later onset, milder skeletal manifestations, smaller elevations of GAGs, and typically a longer lifespan. Estimates of the incidence of MPS VI range from 1 in 250,000 to 1 in 300,000. Treatment options include hematopoietic stem cell transplantation and/or enzyme replacement therapy. Elevations of dermatan and/or heparan sulfate are seen in MPS types I, II, III, and VI. Elevations of keratan sulfate are seen in MPS IV.

**Useful For:** Quantification of heparan sulfate, dermatan sulfate, and keratan sulfate in dried blood spots can support the biochemical diagnosis of 1 of the mucopolysaccharidoses types I, II, III, IV, or VI.

**Interpretation:** Elevations of dermatan sulfate and/or heparan sulfate may be indicative of 1 of the mucopolysaccharidoses types I, II, III, or VI. Elevations of keratan sulfate may be indicative of mucopolysaccharidoses type IV.

**Reference Values:**

<table>
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</tr>
</tbody>
</table>

Mucopolysaccharidosis, Blood Spot

Clinical Information: The mucopolysaccharidoses (MPS) are a group of disorders caused by a deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAGs, also called mucopolysaccharides). Undegraded or partially degraded GAGs are stored in lysosomes and excreted in the urine. Accumulation of GAGs in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in MPS disorders. Depending on the extent of the enzyme deficiency and type of accumulating storage material, MPS patients may present with a variety of clinical findings that can include coarse facial features, cardiac abnormalities, organomegaly, intellectual disabilities, short stature and skeletal abnormalities. MPS I is an autosomal recessive disorder caused by reduced or absent activity of the enzyme alpha-L-iduronidase due to mutations in the IDUA gene. This enzyme deficiency results in a wide range of clinical phenotypes that are further categorized as MPS IH (Hurler syndrome), MPS IS (Scheie syndrome), and MPS IH/S (Hurler-Scheie syndrome), and which cannot be distinguished via biochemical methods. Clinically, they are also referred to as MPS I and attenuated MPS I. MPS IH is the most severe and has an early onset consisting of skeletal deformities, coarse facial features, hepatosplenomegaly, macrocephaly, cardiomyopathy, hearing loss, macroGLOSSIA, and respiratory tract infections. Developmental delay is noticed as early as 12 months, and without treatment, death usually occurs before 10 years of age. MPS IH/S has an intermediate clinical presentation characterized by progressive skeletal symptoms called dysostosis multiplex. Individuals typically have little or no intellectual dysfunction. Corneal clouding, joint stiffness, deafness, and valvular heart disease can develop by early to mid-teens. Survival into adulthood is common. Comparatively, MPS IS presents with the mildest phenotype. The onset occurs after 5 years of age. It is characterized by normal intelligence and stature; however, affected individuals do experience joint involvement, visual impairment, and obstructive airway disease. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS II, Hunter syndrome is an X-linked lysosomal storage disorder caused by a reduced or absent activity of the enzyme iduronate 2-sulfatase. The clinical features and severity of symptoms of MPS II are widely ranging from severe disease to an attenuated form, which generally presents later in life with a milder clinical presentation. In general, symptoms may include coarse facial features, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. The clinical presentation of MPS II is similar to that of MPS I with the notable difference of the lack of corneal clouding in MPS II. Due to the X-linked inheritance pattern, MPS II is observed almost exclusively in males with an estimated incidence of 1 in 170,000 male births. Symptomatic carrier females have been reported, but are very rare. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy MPS-III, Sanfilippo syndrome is caused by a reduced or absent activity of 1 of 4 enzymes involved in heparan sulfate degradation. Patients with MPS III uniformly excrete heparan sulfate resulting in similar clinical phenotypes, and are further classified as type A, B, C, or D based upon the specific enzyme deficiency. Sanfilippo syndrome is characterized by severe central nervous system (CNS) degeneration, but only mild physical disease. Such disproportionate involvement of the CNS is unique among the MPSs. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the 20s. The occurrence of MPS III varies by subtype with types A and B being the most common and types C and D being very rare. The collective incidence is approximately 1 in 58,000 live births. MPS IVA, Morquio syndrome is caused by a reduced or absent N-acetylgalactosamine-6-sulfate sulfatase. Clinical features and severity of symptoms of MPS IVA are widely variable, but may include skeletal dysplasia, short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Estimates of the incidence of MPS IVA syndrome range from 1 in 200,000 to 1 in 300,000 live births. Treatment with enzyme replacement therapy is the only effective treatment available for MPS IVA.

Clinical Information: The mucopolysaccharidoses (MPS) are a group of disorders caused by a deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAGs, also called mucopolysaccharides). Undegraded or partially degraded GAGs are stored in lysosomes and excreted in the urine. Accumulation of GAGs in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in MPS disorders. Depending on the extent of the enzyme deficiency and type of accumulating storage material, MPS patients may present with a variety of clinical findings that can include coarse facial features, cardiac abnormalities, organomegaly, intellectual disabilities, short stature and skeletal abnormalities. MPS I is an autosomal recessive disorder caused by reduced or absent activity of the enzyme alpha-L-iduronidase due to mutations in the IDUA gene. This enzyme deficiency results in a wide range of clinical phenotypes that are further categorized as MPS IH (Hurler syndrome), MPS IS (Scheie syndrome), and MPS IH/S (Hurler-Scheie syndrome), and which cannot be distinguished via biochemical methods. Clinically, they are also referred to as MPS I and attenuated MPS I. MPS IH is the most severe and has an early onset consisting of skeletal deformities, coarse facial features, hepatosplenomegaly, macrocephaly, cardiomyopathy, hearing loss, macroGLOSSIA, and respiratory tract infections. Developmental delay is noticed as early as 12 months, and without treatment, death usually occurs before 10 years of age. MPS IH/S has an intermediate clinical presentation characterized by progressive skeletal symptoms called dysostosis multiplex. Individuals typically have little or no intellectual dysfunction. Corneal clouding, joint stiffness, deafness, and valvular heart disease can develop by early to mid-teens. Survival into adulthood is common. Comparatively, MPS IS presents with the mildest phenotype. The onset occurs after 5 years of age. It is characterized by normal intelligence and stature; however, affected individuals do experience joint involvement, visual impairment, and obstructive airway disease. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. MPS II, Hunter syndrome is an X-linked lysosomal storage disorder caused by a reduced or absent activity of the enzyme iduronate 2-sulfatase. The clinical features and severity of symptoms of MPS II are widely ranging from severe disease to an attenuated form, which generally presents later in life with a milder clinical presentation. In general, symptoms may include coarse facial features, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and regression. The clinical presentation of MPS II is similar to that of MPS I with the notable difference of the lack of corneal clouding in MPS II. Due to the X-linked inheritance pattern, MPS II is observed almost exclusively in males with an estimated incidence of 1 in 170,000 male births. Symptomatic carrier females have been reported, but are very rare. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy MPS-III, Sanfilippo syndrome is caused by a reduced or absent activity of 1 of 4 enzymes involved in heparan sulfate degradation. Patients with MPS III uniformly excrete heparan sulfate resulting in similar clinical phenotypes, and are further classified as type A, B, C, or D based upon the specific enzyme deficiency. Sanfilippo syndrome is characterized by severe central nervous system (CNS) degeneration, but only mild physical disease. Such disproportionate involvement of the CNS is unique among the MPSs. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the 20s. The occurrence of MPS III varies by subtype with types A and B being the most common and types C and D being very rare. The collective incidence is approximately 1 in 58,000 live births. MPS IVA, Morquio syndrome is caused by a reduced or absent N-acetylgalactosamine-6-sulfate sulfatase. Clinical features and severity of symptoms of MPS IVA are widely variable, but may include skeletal dysplasia, short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Estimates of the incidence of MPS IVA syndrome range from 1 in 200,000 to 1 in 300,000 live births. Treatment with enzyme replacement therapy is the only effective treatment available for MPS IVA.
replacement therapy is available. MPS IVB, Morquio B syndrome is caused by a reduced or absent beta-galactosidase activity, which gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms of MPS IVB are widely variable ranging from severe disease to an attenuated form which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. The incidence of MPS IVB is estimated to be about 1 in 250,000 live births. Treatment options are limited to symptomatic management. MPS VI; Maroteaux-Lamy syndrome is an autosomal recessive lysosomal storage disorder caused by the deficiency of the enzyme arylsulfatase B. Clinical features and severity of symptoms are widely variable, but typically include short stature, dysostosis multiplex, facial dysmorphism, stiff joints, claw-hand deformities, carpal tunnel syndrome, hepatosplenomegaly, corneal clouding, and cardiac defects. Intelligence is usually normal. Rapidly progressing forms have an early onset of symptoms, significantly elevated GAGs especially dermatan sulfate, and can lead to death before the second or third decade. A more slowly progressing form has a later onset, milder skeletal manifestations, smaller elevations of GAGs, and typically a longer lifespan. Estimates of the incidence of MPS VI range from 1 in 250,000 to 1 in 300,000. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. Elevations of dermatan and/or heparan sulfate are seen in MPS types I, II, III, and VI. Elevations of keratan sulfate are seen in MPS IV.

**Useful For:** Quantification of heparan sulfate, dermatan sulfate, and keratan sulfate in dried blood spots can support the biochemical diagnosis of one of the mucopolysaccharidoses types I, II, III, IV, or VI.

**Interpretation:** Elevations of dermatan sulfate and/or heparan sulfate may be indicative of one of the mucopolysaccharidoses types I, II, III, or VI. Elevations of keratan sulfate may be indicative of mucopolysaccharidoses type IV.

**Reference Values:**

DERMATAN SULFATE (DS)
- Newborn: < or =2 weeks: < or =200 nmol/L
- >2 weeks: < or =130 nmol/L

HEPARAN SULFATE (HS)
- Newborn: < or =2 weeks: < or =96 nmol/L
- >2 weeks: < or =95 nmol/L

TOTAL KERATAN SULFATE (KS)
- < or =5 years: < or =1,900 nmol/L
- 6-10 years: < or =1,750 nmol/L
- 11-15 years: < or =1,500 nmol/L
- >15 years: < or =750 nmol/L

**Clinical References:**

**MUC 82675**

**Mucor, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


**Mugwort, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Mulberry, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
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<td>3.50-17.4</td>
<td>Positive</td>
</tr>
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</table>

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**MRDMM** 65218

**Multiple Myeloma Minimal Residual Disease by Flow, Bone Marrow**

**Clinical Information:** Multiple myeloma is an incurable malignant neoplasm of plasma cells. One of the best prognostic factors in multiple myeloma is the level of minimal residual disease post chemotherapy or autologous stem cell transplantation. The greater depth of the response (less malignant cells present), the longer time to progression and overall survival. (1)

**Useful For:** Detection of low level (minimal residual disease) myeloma cells after therapy

**Interpretation:** The interpretation of the test is done by an evaluating automated and manually gated populations to isolate abnormal plasma cells. If there is an abnormal plasma cell population (cluster of 20 cells or more), then the result is minimal residual disease (MRD)-positive, with the percentage of abnormal plasma cells out of total analyzed events. If no abnormal population is found, then the result will be interpreted as MRD-negative.

**Reference Values:**
An interpretive report will be provided. This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and correlation with the previous patient history will be provided by a hematopathologist for every case.


**MSP2** 83305

**Multiple Sclerosis (MS) Profile**

**Clinical Information:** Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease characterized by visual, motor, and sensory disturbances. The diagnosis of MS is dependent on clinical, radiological, and laboratory findings. The detection of increased intrathecal immunoglobulin (Ig) synthesis is the basis for current diagnostic laboratory tests for MS. These tests include the cerebrospinal fluid (CSF) IgG index and CSF oligoclonal band detection.

**Useful For:** Diagnosing multiple sclerosis, especially helpful in patients with equivocal clinical or radiological findings

**Interpretation:** Oligoclonal banding (OCB): A finding of 4 or more cerebrospinal fluid (CSF)-specific
bands (ie, bands that are present in CSF, but are absent in serum) is consistent with multiple sclerosis (MS). CSF IgG index: >0.85 is consistent with MS. Abnormal CSF IgG indexes and OCB patterns have been reported in 70% to 80% of patients with MS. If both tests are performed, at least 1 of the tests has been reported to be positive in more than 90% of patients with MS. A newer methodology for OCB detection, isoelectric focusing, is utilized in this test and has been reported to be more sensitive (90%-95%). The presence of OCB or elevated CSF IgG index is unrelated to disease activity.

**Reference Values:**

**OLIGOCOLONAL BANDS**

<4 bands

CSF INDEX

<table>
<thead>
<tr>
<th>CSF IgG index</th>
<th>0.00-0.85</th>
</tr>
</thead>
</table>

CSF IgG: 0.0-8.1 mg/dL

CSF albumin: 0.0-27.0 mg/dL

Serum IgG

<table>
<thead>
<tr>
<th>Age Range</th>
<th>serum IgG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 months</td>
<td>100-334 mg/dL</td>
</tr>
<tr>
<td>5-8 months</td>
<td>164-588 mg/dL</td>
</tr>
<tr>
<td>9-14 months</td>
<td>246-904 mg/dL</td>
</tr>
<tr>
<td>15-23 months</td>
<td>313-1,170 mg/dL</td>
</tr>
<tr>
<td>2-3 years</td>
<td>295-1,156 mg/dL</td>
</tr>
<tr>
<td>4-6 years</td>
<td>386-1,470 mg/dL</td>
</tr>
<tr>
<td>7-9 years</td>
<td>462-1,682 mg/dL</td>
</tr>
<tr>
<td>10-12 years</td>
<td>503-1,719 mg/dL</td>
</tr>
<tr>
<td>13-15 years</td>
<td>509-1,580 mg/dL</td>
</tr>
<tr>
<td>16-17 years</td>
<td>487-1,327 mg/dL</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td>767-1,590 mg/dL</td>
</tr>
</tbody>
</table>

Serum albumin: 3,200-4,800 mg/dL

CSF IgG/albumin: 0.0-0.21

Serum IgG/albumin: 0.00-0.40

CSF IgG synthesis rate: 0-12 mg/24 hours

**Clinical References:**


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**SUMFZ 35559**

**Multiple Sulfatase Deficiency, Full Gene Analysis**

**Clinical Information:** Multiple sulfatase deficiency (MSD) is a rare autosomal recessive lysosomal storage disorder (LSD) caused by mutations in the sulfatase-modifying factor 1 (SUMF1) gene. SUMF1 encodes for a formylglycine-generating enzyme (FGE) that performs a critical posttranslational modification of the catalytic residue necessary for activation of all human sulfatases. MSD is often confused for a single sulfatase deficiency because it is characterized by deficiency of all known sulfatases, which results in tissue accumulation of sulfatides, sulfated glycoaminoglycans, sphingolipids, and steroid sulfates. Indeed, the clinical phenotype encompasses symptoms of every single sulfatase deficiency, including metachromatic leukodystrophy (MLD), the mucopolysaccharidoses, X-linked ichthyosis, and chondrodysplasia punctata type I. Age of onset and clinical severity are variable and correspond with the level of residual FGE enzyme activity. A severe neonatal form of MSD closely overlaps the clinical presentation of the mucopolysaccharidoses but it is often fatal within 1 year. Late-infantile MSD (onset 0-2 years) accounts for most cases and is characterized by a clinical presentation similar to MLD. Patients show progressive cognitive and motor impairment as well as skeletal changes. More rarely, MSD presents in late childhood (juvenile-onset) with more mild symptoms and slower progression. Patients with late-infantile or juvenile-onset MSD may have less severe sulfatase deficiency. Patients with a clinical suspicion of MLD, a mucopolysaccharidosis, X-linked ichthyosis, or chondrodysplasia should be investigated for possible FGE deficiency. Urine sulfatide analysis is the recommended first tier biochemical test (CTSA /
Ceramide Trihexoside/Sulfatide Accumulation in Urine Sediment, Urine). If positive, iduronate sulfatase and arylsulfatase A and B enzyme levels should be assayed and are typically decreased in patients with MSD. While enzyme replacement therapy has been used to treat a subset of single LSD, its effectiveness is not well established for patients with MSD. Therefore, confirmation or exclusion of a diagnosis of MSD has important implications for patient management as well as prognosis.

**Useful For:** Confirmation of multiple sulfatase deficiency for patients with clinical features
Identification of SUMF1 mutation to allow for genetic testing in family members

**Interpretation:** All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics (AMCG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**MUM1B**

**MUM-1/IRF4 Immunostain, Bone Marrow, Technical Component Only**

**Clinical Information:** Multiple myeloma oncogene-1 (MUM-1) is expressed in the nucleus of a subset of B cells in the light zone of the germinal center (representing late stages of B-cell differentiation), plasma cells, activated T cells, and a variety of hematolymphoid neoplasms derived from these cells. Among nonhematolymphoid neoplasms, MUM-1 expression has been reported in melanomas.

**Useful For:** Aiding in the identification of hematolymphoid neoplasms and melanomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
**MUM1**

**70514**

**MUM-1/IRF4 Immunostain, Technical Component Only**

**Clinical Information:** Multiple myeloma oncogene-1 (MUM-1) is expressed in the nucleus of a subset of B cells in the light zone of the germinal center (representing late stages of B-cell differentiation), plasma cells, activated T cells, and a variety of hematolymphoid neoplasms derived from these cells. Among nonhematolymphoid neoplasms, MUM-1 expression has been reported in melanomas.

**Useful For:** Aids in the identification of hematolymphoid neoplasms and melanomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**CMUMP**

**81435**

**Mumps Virus Antibodies, IgG and IgM (Separate Determinations), Spinal Fluid**

**Clinical Information:** There is only 1 serotype of mumps virus that infects humans. Mumps has been recognized since antiquity by virtue of the parotitis that is often a striking clinical feature of the disease. Generally, a trivial childhood illness, the varied presentation of mumps reflects the widespread invasion of visceral organs and central nervous system that commonly follows infection with mumps virus.

**Useful For:** Aiding in the diagnosis of central nervous system infection by mumps virus

**Interpretation:** Detection of organism-specific antibodies in the cerebrospinal fluid (CSF) may suggest central nervous system infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of central nervous system infection.

**Reference Values:**
- IgG: <1:5
- IgM: <1:10

Reference values apply to all ages.


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**MPPG**

**34947**

**Mumps Virus Antibody, IgG, Serum**

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Clinical Information: The mumps virus is a member of the Paramyxoviridae family of viruses, which include parainfluenza virus serotypes 1-4, measles, respiratory syncytial virus (RSV), and metapneumovirus. Mumps is highly infectious among unvaccinated individuals and is typically transmitted through inhalation of infected respiratory droplets or secretions. Following an approximately 2-week incubation period, symptom onset is typically acute with a prodrome of low-grade fever, headache, and malaise.(1,2) Painful enlargement of the salivary glands, the hallmark of mumps, occurs in approximately 60% to 70% of infections and in 95% of patients with symptoms. Testicular pain (orchitis) occurs in approximately 15% to 30% of postpubertal men and abdominal pain (oophoritis) is found in 5% of postpubertal women.(1) Other complications include mumps-associated pancreatitis (<5% of cases) and central nervous system disease (meningitis <10% and encephalitis <1%). Widespread routine immunization of infants with attenuated mumps virus has dramatically decreased the number of reported mumps cases in the United States. However, outbreaks continue to occur, indicating persistence of the virus in the general population. Laboratory diagnosis of mumps is typically accomplished by detection of IgM- and IgG-class antibodies to the mumps virus. However, due to the widespread mumps vaccination program, in clinically suspected cases of acute mumps infection, serologic testing should be supplemented with virus isolation in culture or detection of viral nucleic acid by PCR in throat, saliva, or urine specimens.

Useful For: Determination of postimmunization immune response of individuals to the mumps vaccine Documentation of previous infection with mumps virus in an individual with no previous record of immunization to mumps virus

Interpretation: Positive: The presence of detectable IgG-class antibodies indicates prior exposure to the mumps virus through infection or immunization. Individuals testing positive are considered immune to mumps virus. Equivocal: Submit an additional specimen for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative: The absence of detectable IgG-class antibodies suggests no prior exposure to the mumps virus or the lack of a specific immune response to immunization.

Reference Values:
Vaccinated: Positive (> or = 1.1 AI)
Unvaccinated: Negative (< or = 0.8 AI)
Reference values apply to all ages.

Useful For: Diagnosis of mumps virus infection. Determination of postimmunization immune response of individuals to the mumps vaccine. Documentation of previous infection with mumps virus in an individual with no previous record of immunization to mumps virus.

Interpretation: A positive IgG result coupled with a positive IgM result suggests recent infection with mumps virus. This result should not be used alone to diagnose mumps infection and should be interpreted in the context of clinical presentation. A positive IgG result coupled with a negative IgM result indicates previous vaccination to or infection with mumps virus. These individuals are considered to have protective immunity to reinfection. A negative IgG result coupled with a negative IgM result indicates the absence of prior exposure to mumps virus and nonimmunity. However, a negative result does not rule-out mumps infection or response to vaccination. The specimen may have been drawn before the appearance of detectable antibodies. Negative results in suspected early mumps infection or within a week following vaccination should be followed by testing a new serum specimen in 2 to 3 weeks. Equivocal results should be followed up with testing of a new serum specimen within 10 to 14 days.

Reference Values:
IgM:
- Negative
  - Index value 0.00-0.79 = negative
- Reference values apply to all ages.

IgG:
- Vaccinated: Positive (> or =1.1 AI)
- Unvaccinated: Negative (< or =0.8 AI)
- Reference values apply to all ages.

Clinical References:

Mumps Virus Antibody, IgM, Serum

Clinical Information: Mumps virus, together with parainfluenza types 1 through 4, respiratory syncytial virus, and measles virus are classified in the family Paramyxoviridae. Mumps is an acute infection that causes the painful enlargement of the salivary glands in approximately 70% to 90% of children (4-15 years of age) who develop clinical disease.(1) In 5% to 20% of postpubertal individuals, testicular pain (orchitis in males) and abdominal pain (oophoritis in females) can occur. Other complications include pancreatitis (<5% of cases) and central nervous system disease (meningitis/encephalitis) that occur rarely (about 1 in 6,000 cases of mumps). Widespread routine immunization of infants with attenuated mumps virus has changed the epidemiology of this virus infection. Since 1989, there has been a steady decline in reported mumps cases, with an average of 265 cases each year since 2001. However, a recent outbreak of mumps in 2006 reemphasized that this virus continued to persist in the population, and laboratory testing may be needed in clinically compatible situations. The laboratory diagnosis of mumps is typically accomplished by detection of antibody to mumps virus. However, due to the limitations of serology (eg, inadequate sensitivity and specificity), additional laboratory testing including virus isolation or detection of viral nucleic acid by PCR in throat, saliva, or urine specimens should be considered in clinically compatible situations.

Useful For: Laboratory diagnosis of mumps virus infection

Interpretation: Positive: presence of IgM-class antibodies to mumps virus may support a clinical diagnosis of recent/acute phase infection with this virus. Negative: absence of IgM-class antibodies to mumps virus suggests lack of acute phase infection with mumps virus. However, serology may be negative in early disease, and results should be interpreted in the context of clinical findings.

Reference Values:
Negative
Index value 0.00-0.79 = negative
Reference values apply to all ages.


FMTAG

Murine Typhus Antibodies, IgG
Clinical Information: A fourfold increase in antibody titer between acute and convalescent specimens is consistent with recent infection. A single titer \(>1:128\) can be consistent with recent infection. Titers of \(1:16 - 1:64\) can be indicative of recent or past infection.

Useful For: Detect antibodies following infection with murine typhus.

Reference Values:
Reference Interval:
- Negative: <1:64
- Present or Past: 1:64
- Recent/Active: >1:64

MBX

Muscle Pathology Consultation
Clinical Information: In our consultative practice, we strive to bring the customer the highest quality of diagnostic neuromuscular pathology, aiming to utilize only those ancillary tests that support the diagnosis in a cost-effective manner, and to provide a rapid turnaround time for diagnostic results.

Useful For: Obtaining a rapid, expert opinion on muscle biopsy specimens for neuromuscular disease

Interpretation: Results are reported in a formal neuromuscular pathology report that includes an interpretive comment, if necessary. The formal pathology report is faxed or sent by mail according to the preference of the referring institution.

Reference Values:
An interpretive report will be provided.


MUSK

Muscle-Specific Kinase (MuSK) Autoantibody, Serum
Clinical Information: Fatigable weakness due to impaired synaptic transmission at the neuromuscular junction is characteristic of myasthenia gravis (MG). The diagnosis is made by clinical and electromyographic criteria. Positive autoimmune serology must be interpreted in the clinical and electrophysiological context and response to anticholinesterase medication. Most cases are autoimmune and are caused by IgG autoantibodies binding to critical postsynaptic membrane molecules (nicotinic acetylcholine receptor or its interacting proteins).(1) Autoantibody detection frequency is lowest in patients with weakness confined to extraocular muscles (71% muscle acetylcholine receptor: AChR binding).(2) Mayo Clinic’s first-line serological evaluation detects muscle AChR antibody in 92% of nonimmunosuppressed patients with generalized weakness due to MG. Muscle-specific kinase (MuSK) antibody is detectable in more than one-third of those seronegative for muscle AChR antibody (less than 4% of all patients).(3) Physiologically, MuSK is involved in integrating and stabilizing AChR clusters in the motor endplate. MuSK is activated when the nerve-derived proteoglycan agrin binds to its receptor, lipoprotein-related protein 4 (LRP4). Antibodies to LRP4 itself have been described in rare patients.(1)
Six percent of nonimmunosuppressed patients with generalized MG lack demonstrable AChR or MuSK antibodies (double seronegative). Other rare autoantibodies no doubt remain to be discovered in such cases. However, as in autoimmune AChR MG and MuSK MG, testing for common organ-specific and nonorgan-specific autoantibodies is a valuable ancillary investigation in evaluating seronegative acquired generalized MG. General serological testing, coupled with family or personal history, will disclose autoimmune phenomena in 77% of those cases.(3) These disorders may include thyroid disease, type 1 diabetes, vitiligo, premature greying, rheumatoid arthritis, or lupus. Testing may also reveal antinuclear antibodies, glutamic acid decarboxylase (GAD65) antibodies, thyroperoxidase/thyroglobulin antibodies, or gastric parietal cell antibodies.(3) Objective improvement in strength following a therapeutic trial of plasmapheresis or intravenous immune globulin would justify consideration of long-term immunosuppression. Females are generally affected by autoimmune MuSK MG more often than males. Onset can occur at any age (pediatric to elderly). Patients may derive limited benefit from anticholinesterase medication. The thymus is normal, and patients are generally not benefited by thymectomy. Antibody-lowering therapies are effective. Bulbar, facial, and respiratory weakness are prominent, and crises are common.(1,4)

**Useful For:** Diagnosis of autoimmune muscle-specific kinase (MuSK) myasthenia gravis
- Second-order test to aid in the diagnosis of autoimmune myasthenia gravis when first-line serologic tests are negative
- Establishing a quantitative baseline value for MuSK antibodies that allows comparison with future levels if weakness is worsening

**Interpretation:** A positive result, in the appropriate clinical context, confirms the diagnosis of autoimmune muscle-specific kinase myasthenia gravis. Seropositivity justifies consideration of immunotherapy.

**Reference Values:**
< or =0.02 nmol/L

**Clinical References:**

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**Muscular Dystrophy Panel (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
- This is not an orderable test.

**Mushroom IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.
MUSH
82626

Mushroom, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>&gt; or =100</td>
<td></td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


FMTFG
57679

Mustard Food IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.
**Mustard, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**Reference values apply to all ages.**


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**FOKFM**

**Mutation- Specific testing- One known familial mutation**

**Reference Values:**

An interpretive report will be provided.

**MYHZ**

**MUTYH Gene, Full Gene Analysis**

**Clinical Information:** Biallelic germline mutations in the MUTYH gene (also known as MYH) cause MUTYH-associated polyposis (MAP) syndrome, an autosomal recessive form of hereditary colorectal cancer. MAP is a polyposis syndrome typically associated with 10 to 100 adenomatous colon polyps.

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
polyps, which in turn confer a significantly increased risk for colorectal cancer. Therefore, phenotypic overlap exists between MAP and attenuated familial adenomatous polyposis (FAP). However, the number of cumulative polyps is variable and can mimic both classic FAP, associated with hundreds to thousands of polyps, and Lynch syndrome, which is generally associated with very few (1-5) adenomatous polyps. Therefore, evaluation for MUTYH should be considered in patients with early onset colorectal cancer in whom a DNA mismatch repair (MMR) defect has not been identified. Patients with biallelic MUTYH mutations are at risk for extracolonic manifestations including upper gastrointestinal polyps or cancer as well as other tumors. Congenital hyperpigmentation of the retinal epithelium (CHRPE), dental anomalies, dermal cysts, desmoid tumors, and osteomas may also occur, but to a lesser extent than what is observed in patients with FAP. Literature suggests that monoallelic carriers may also be at increased risk for colon, gastric, breast, and endometrial cancer. Approximately 1% to 2% of mixed European Caucasian individuals are predicted to carry a MUTYH mutation. Therefore, the reproductive partners of monoallelic and biallelic carriers should be offered carrier screening to adequately assess the risk of their offspring to have MAP. Two mutations, G396D and Y179C (originally known as G382D and Y165C), account for approximately 85% of the disease-causing MUTYH mutations in affected mixed European Caucasian individuals.

**Useful For:** Confirmation of suspected clinical diagnosis of MUTYH-associated polyposis (MAP) in patients with adenomatous polyps or early-onset colorectal cancer Identification of familial MUTYH mutations to allow for predictive or diagnostic testing in family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.


**FBLAS**

<table>
<thead>
<tr>
<th>MVista Blastomyces Quantitative Antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interpretation:</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Reference Values:</strong></td>
</tr>
<tr>
<td>Reference Value: None Detected</td>
</tr>
<tr>
<td>Results reported as ng/mL in 0.2 - 14.7 ng/mL range</td>
</tr>
<tr>
<td>Results above the limit of detection but below 0.2 ng/mL are reported as 'Positive, Below the Limit of Quantification'</td>
</tr>
<tr>
<td>Results above 14.7 ng/mL are reported as 'Positive, Above the Limit of Quantification'</td>
</tr>
</tbody>
</table>

**FMVCO**

<table>
<thead>
<tr>
<th>MVista Coccidioides Antigen EIA</th>
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</thead>
<tbody>
<tr>
<td><strong>Reference Values:</strong></td>
</tr>
<tr>
<td>Reference interval: None Detected</td>
</tr>
<tr>
<td>Results reported as ng/mL in 0.07 - 8.2 ng/mL range</td>
</tr>
<tr>
<td>Results above 8.2 ng/mL are reported as ‘Positive, Above the Limit of Quantification’</td>
</tr>
</tbody>
</table>
**MVista Histoplasma Ag Quantitative EIA**

**Reference Values:**
Reference interval: None Detected

Results reported as ng/mL in 0.4 to 19 ng/mL range

Results above the limit of detection but below 0.4 ng/mL are reported as Positive, Below the Limit of Quantification.

Results above 19.0 ng/mL are reported as Positive, Above the Limit of Quantification.

**MVista Histoplasma Ag Quantitative, Serum**

**Reference Values:**
Reference interval: None Detected

Results reported as ng/mL in 0.4 to 19.0 ng/mL range

Results above the limit of detection, but below 0.4 ng/mL are reported as 'Positive, Below the Limit of Quantitation'.

Results above 19.0 ng/mL are reported as 'Positive, Above the Limit of Quantitation'.

**MVista Histoplasma Ag Quantitative, Spinal Fluid**

**Reference Values:**
Reference interval: None Detected

Results reported as ng/mL in 0.4 to 19 ng/mL range

Results above the limit of detection by below 0.4 ng/mL are reported as 'Positive, Below the Limit of Quantification'.

Results above 19.0 ng/mL are reported as 'Positive, Above the Limit of Quantification'.

**Myasthenia Gravis (MG) Evaluation with MuSK Reflex, Serum**

**Clinical Information:** Fatigable weakness due to impaired synaptic transmission at the neuromuscular junction is characteristic of myasthenia gravis (MG). The diagnosis is made by clinical and electromyographic criteria. Positive autoimmune serology must be interpreted in the clinical and electrophysiological context and response to anticholinesterase medication. Most cases are autoimmune and are caused by IgG autoantibodies binding to critical postsynaptic membrane molecules (nicotinic acetylcholine receptor or its interacting proteins, such as muscle-specific kinase: MuSK).

Autoantibody detection frequency is lowest in patients with weakness confined to extraocular muscles (71% muscle acetylcholine receptor: AChR binding). Mayo Clinic's first-line serological evaluation detects muscle AChR antibody in 92% of nonimmunosuppressed patients with generalized weakness due to MG. In adults with MG there is at least a 20% occurrence of thymoma or other neoplasm. If acetylcholine receptor (AChR) modulating antibodies are greater than or equal to 90% and striational antibodies are greater than or equal to 1:120, then there is an increased risk of thymoma, and AChR ganglionic neuronal autoantibody, glutamic acid decarboxylase autoantibody, neuronal voltage-gated potassium channel autoantibody, and collapsin response-mediated response-5-IgG may also be detected in that paraneoplastic context. MuSK antibody is detectable in more than one-third of those seronegative for muscle AChR antibody (<4% of all patients). Physiologically, MuSK is involved in...
in integrating and stabilizing AChR clusters in the motor endplate. MuSK is activated when the nerve-derived proteoglycan agrin binds to its receptor, lipoprotein-related protein 4 (LRP4). Antibodies to LRP4 itself have been described in rare patients. Females are generally affected by autoimmune MuSK MG more often than males. Onset can occur at any age (pediatric to elderly). Patients may derive limited benefit from anticholinesterase medication. The thymus is normal, and patients are generally not benefited by thymectomy. Antibody-lowering therapies are effective. Bulbar, facial, and respiratory weakness are prominent, and crises are common. Six percent of nonimmunosuppressed patients with generalized MG lack demonstrable AChR or MuSK antibodies (double seronegative). However, as in autoimmune AChR MG and MuSK MG, testing for common organ-specific and nonorgan-specific autoantibodies is a valuable ancillary investigation in evaluating seronegative acquired generalized MG. General serological testing, coupled with family or personal history, will disclose autoimmune phenomena in 77% of those cases. These disorders may include thyroid disease, type 1 diabetes, vitiligo, premature greying, rheumatoid arthritis, or lupus. Objective improvement in strength following a therapeutic trial of plasmapheresis or intravenous immune globulin would justify consideration of long-term immunosuppression.

**Useful For:** Diagnosis for autoimmune myasthenia gravis in adults and children Distinguishing autoimmune from congenital myasthenia gravis in adults and children Establishing a quantitative baseline value that allows comparison with future levels if weakness is worsening

**Interpretation:** A positive result, in the appropriate clinical context, confirms the diagnosis of autoimmune myasthenia gravis, with or without thymoma. Seropositivity justifies consideration of immunotherapy.

**Reference Values:**

**ACh RECEPTOR (MUSCLE) BINDING ANTIBODY**

< or = 0.02 nmol/L

**ACh RECEPTOR (MUSCLE) MODULATING ANTIBODIES**

0-20% (reported as __% loss of AChR)

**STRIATIONAL (STRIATED MUSCLE) ANTIBODIES**

<1:120

**Clinical References:**


**Myasthenia Gravis (MG) Evaluation, Adult**

**Clinical Information:** Myasthenia gravis (MG) is an acquired disorder of neuromuscular transmission caused by the binding of pathogenic autoantibodies to muscle's postsynaptic nicotinic acetylcholine receptor (AChR). In a small minority of patients the pathogenic antibody is directed at the muscle-specific receptor tyrosine kinase (MuSK) antigen. The ensuing weakness in both cases reflects a critical loss of the AChR channel protein, which is required to activate the muscle action potential. MG affects children (see MGP1 / Myasthenia Gravis [MG] Evaluation, Pediatric) as well as adults. In adults with MG there is at least a 20% occurrence of thymoma or other neoplasm. Neoplasms are an endogenous source of the antigens driving production of autoantibodies. Autoimmune serology is indispensable for initial evaluation and monitoring of patients with acquired disorders of neuromuscular transmission. The neurological diagnosis depends on the clinical context and electromyographic findings, and is confirmed more readily by the individual patient's serological profile than by any single test. Not all of the antibodies detected in this profile impair neuromuscular transmission (eg, antibodies directed at cytoplasmic epitopes...
accessible on solubilized AChR, or sarcomeric proteins that constitute the striational antigens. If muscle acetylcholine receptor (AChR) modulating antibody value is (or exceeds) 90% AChR loss and striational antibody is detected, thymoma is likely. Reflexive testing will include collapsin response-mediated protein-5-lgG Western blot, ganglionic AChR antibody, glutamic acid decarboxylase (GAD65) antibody, and voltage-gated potassium channel complex (VGKC) antibody (which are frequent with thymoma). Note: Single antibody tests may be requested in follow-up of patients with positive results documented in this laboratory. See Myasthenia Gravis: Adult Diagnostic Algorithm in Special Instructions.

**Useful For:** Initial evaluation of patients aged 20 or older with symptoms and signs of acquired myasthenia gravis (MG) Bone marrow transplant recipients with suspected graft-versus-host disease, particularly if weakness has appeared Confirming that a recently acquired neurological disorder has an autoimmune basis (eg, MG) Providing a quantitative baseline for future comparisons in monitoring a patient's clinical course and the response to immunomodulatory treatment Raising likelihood of neoplasia

**Interpretation:** The patient's autoantibody profile is more informative than the result of any single test for supporting a diagnosis of myasthenia gravis (MG), and for predicting the likelihood of thymoma (see MGT1 / Myasthenia Gravis [MG] Evaluation, Thymoma). Muscle acetylcholine receptor (AChR) and striational autoantibodies are characteristic but not diagnostic of MG. One or both are found in 13% of patients with Lambert-Eaton Syndrome (LES), but P/Q-type calcium channel autoantibodies are very rare in MG. Results are sometimes positive in patients with neoplasia without evidence of neurological impairment. Titers are generally higher in patients with severe weakness, or with thymoma, but severity cannot be predicted by antibody titer. Test results for muscle acetylcholine receptor and striational antibodies may be negative for 6 to 12 months after MG symptom onset. Only 8% of nonimmunosuppressed patients with generalized MG remain seronegative beyond 12 months for all autoantibodies in the adult MG evaluation. Of those patients 38% will have the alternative muscle-specific receptor tyrosine kinase (MuSK)-specific autoantibody. MuSK antibody-positive patients lack thymoma, and have predominantly ocular-bulbar symptoms that respond to plasmapheresis and immunosuppressant therapy. They do not benefit from thymectomy.

**Reference Values:**

**ACh RECEPTOR (MUSCLE) BINDING ANTIBODY**

< or =0.02 nmol/L

**ACh RECEPTOR (MUSCLE) MODULATING ANTIBODIES**

0-20% (reported as ___% loss of AChR)

**STRIATIONAL (STRIATED MUSCLE) ANTIBODIES**

<1:120


**Myasthenia Gravis (MG) Evaluation, Pediatric**

**Clinical Information:** Myasthenia gravis (MG) is an acquired disorder of neuromuscular transmission caused by the binding of pathogenic autoantibodies to muscle's postsynaptic nicotinic acetylcholine receptor (AChR). In about 3% of cases the pathogenic antibody is directed at the functionally associated muscle-specific receptor tyrosine kinase (MuSK). The outcome is a critical loss of the AChR channel protein, which is required to activate the muscle action potential. Amongst North
American Caucasian children (ie, aged 1-18), MG affects prepubertal boys and girls with equal frequency. Spontaneous remissions are relatively frequent. Females predominate (4.5:1) after puberty. Amongst black children with MG, females predominate (2:1) in all age groups, and remissions are infrequent, regardless of therapy. Congenital MG is a hereditary nonautoimmune disorder characterized by defects in AChR or other synaptic proteins. Autoimmune serology is indispensable for both initial evaluation and monitoring the course of patients with acquired disorders of neuromuscular transmission. The neurological diagnosis depends on the clinical context, electromyographic findings, and response to anticholinesterase administration. MG is confirmed more readily by a serological profile than by any single test. Note: Single antibody tests may be requested in follow-up of patients with positive results documented in this laboratory. See Myasthenia Gravis: Pediatric Diagnostic Algorithm in Special Instructions.

**Useful For:** Recommended for initial investigation of patients presenting at less than age 20 with a defect of neuromuscular transmission Confirming that a recently acquired neurological disorder has an autoimmune basis Distinguishing acquired myasthenia gravis from congenital myasthenic syndromes (persistently seronegative) Providing a quantitative baseline for future comparisons in monitoring clinical course and response to immunomodulatory treatment

**Interpretation:** Muscle acetylcholine receptor (AChR) autoantibodies are characteristic but not diagnostic of myasthenia gravis (MG). They are found in 13% of patients with Lambert-Eaton Syndrome (LES), which is rare in children. The patient's autoantibody profile is more informative than the result of any single test for supporting a diagnosis of MG. Titers of AChR antibodies are generally higher in patients with severe weakness, but severity cannot be predicted by antibody titer. Seronegativity is more frequent in children with prepubertal onset of acquired MG (33%-50%) than in adults (<10%). Thymoma is rare under age 20, and striational antibodies (see STR / Striational [Striated Muscle] Antibodies, Serum) also are rare, except in the context of MG related to neoplasia (usually thymoma or neuroblastoma), graft-versus-host disease, autoimmune liver disease, or D-penicillamine therapy. This laboratory has recently noted muscle-specific receptor tyrosine kinase antibody in children with "seronegative" acquired MG, but the frequency of this antibody in pediatric MG has not been determined.

**Reference Values:**
- **ACh RECEPTOR (MUSCLE) BINDING ANTIBODY**
  - ≤0.02 nmol/L
- **ACh RECEPTOR (MUSCLE) MODULATING ANTIBODIES**
  - 0-20% (reported as __% loss of AChR)

**Clinical References:**

**Myasthenia Gravis (MG) Evaluation, Thymoma**

**Clinical Information:** Myasthenia gravis (MG) is an acquired disorder of neuromuscular transmission caused by the binding of pathogenic autoantibodies to muscle's postsynaptic nicotinic acetylcholine receptor (AChR). Synaptic transmission fails when these pathogenic autoantibodies cause a critical loss of the AChR cation channel protein, which is required to activate the muscle action potential. It is estimated that approximately 20% of adult patients have a paraneoplastic basis for MG. Thymoma is the most common neoplasm, often occult at the onset of MG, its diagnosis may precede MG onset. Thymoma is thought to be an endogenous source of muscle and neuronal antigens that drive production of characteristic autoantibodies. Other autoimmune neurological disorders sometimes accompany thymoma, with and without MG, including neuromuscular hyperexcitability, autonomic neuropathy, especially gastrointestinal dysmotilities encephalopathy, subacute hearing loss, or polymyositis. MG can affect
children as well as adults, but a paraneoplastic context is rare in children (neuroblastoma or thymoma are sometimes found). Some of the antibodies in this profile are not pathogenic (eg, antibodies directed at cytoplasmic epitopes accessible in solubilized ion channels, or sarcomeric proteins that constitute the striational antigens). Autoimmune serology is indispensable for initial evaluation and monitoring the course of patients with acquired MG. The neurological diagnosis depends on the clinical context, electromyographic findings, and response to anticholinesterase administration. MG is confirmed more readily by the individual patient's serological profile than by any single test. See Myasthenia Gravis: Thymoma Diagnostic Algorithm in Special Instructions.

**Useful For:** Investigating patients with suspected or proven thymoma, whether or not symptoms or signs of myasthenia gravis (MG) are present Serially monitoring patients for recurrence or metastasis after removal of thymoma Providing a quantitative autoantibody baseline for future comparisons in monitoring a patient's clinical course and the response to thymectomy and immunomodulatory treatment Assessing the likelihood of occult thymoma in a patient with an acquired disorder of neuromuscular or autonomic transmission Evaluating bone marrow transplant recipients with suspected graft-versus-host disease, particularly if there is evidence of weakness Confirming that a recently acquired neurological disorder has an autoimmune basis (eg, MG or dysautonomia)

**Interpretation:** A patient's autoantibody profile is more informative than the result of any single test for predicting the likelihood of thymoma, and for supporting a diagnosis of myasthenia gravis (MG) or other paraneoplastic neurological complication. Muscle acetylcholine receptor (AChR) and striational autoantibodies are characteristic but not diagnostic of MG in the context of thymoma. One or more antibodies in the MG/thymoma evaluation are positive in more than 60% of nonimmunosuppressed patients who have thymoma without evidence of any neurological disorder. Titers of muscle AChR and striational antibodies are generally higher in MG patients who have thymoma, but severity of weakness cannot be predicted by antibody titer. A rising antibody titer (or appearance of a new antibody specificity) following thymoma ablation suggests thymoma recurrence or metastasis, or development of an unrelated neoplasm. Antibodies specific for the alternative muscle autoantigen of MG, muscle-specific receptor tyrosine kinase, are not associated with thymoma.

**Reference Values:**

**ACh RECEPTOR (MUSCLE) BINDING ANTIBODY**
< or =0.02 nmol/L

**ACh RECEPTOR (MUSCLE) MODULATING ANTIBODIES**
0-20% (reported as __% loss of AChR)

**STRIATIONAL (STRIATED MUSCLE) ANTIBODIES**
<1:120

**CRMP-5-IgG WESTERN BLOT**
Negative

**AChR GANGLIONIC NEURONAL ANTIBODY**
< or =0.02 nmol/L

**NEURONAL (V-G) K+ CHANNEL AUTOANTIBODY**
< or =0.02 nmol/L

**GAD65 ANTIBODY ASSAY**
< or =0.02 nmol/L


**Myasthenia Gravis (MG)/Lambert-Eaton Syndrome (LES) Evaluation**

**Clinical Information:** Myasthenia gravis (MG) and Lambert-Eaton syndrome (LES) are acquired disorders of neuromuscular transmission. MG is caused by pathogenic autoantibodies binding to muscle's nicotinic acetylcholine receptor (AChR) or, in a small minority of patients, muscle-specific receptor tyrosine kinase (MuSK); LES is caused by autoantibodies binding to motor nerve terminal's voltage-gated P/Q-type calcium channel. Synaptic transmission fails when autoantibodies cause a critical loss of junctional cation channel proteins that activate the muscle action potential. Both MG and LES can affect children (see MGP1 / Myasthenia Gravis [MG] Evaluation, Pediatric) as well as adults, although LES is very rare in children. In adults MG is 10 times more frequent than LES, but it is sometimes difficult to distinguish the 2 disorders, clinically and electromyographically. In adults with MG, there is at least a 20% occurrence of thymoma or other neoplasm. Neoplasms associated with LES or MG are an endogenous source of the antigens driving production of the autoantibodies that characterize each disorder. LES is frequently associated with small-cell lung carcinoma (SCLC). Thus far, MuSK antibody has not been associated with any neoplasm. Autoimmune serology is indispensable for both the initial evaluation and monitoring of patients with acquired disorders of neuromuscular transmission. The neurological diagnosis depends on the clinical context and electromyographic findings, and is confirmed more readily by a serological profile than by any single test. Not all of the antibodies in this profile impair neuromuscular transmission (eg, N-type calcium channel antibodies, antibodies directed at cytoplasmic epitopes accessible in detergent solubilized P/Q-type calcium channels and muscle AChRs, or antibodies against sarcomeric proteins that constitute the striational antigens). Note: Single antibody tests may be requested in the follow-up of patients with positive results previously documented in this laboratory. See Myasthenia Gravis/Lambert Eaton Syndrome Diagnostic Algorithm in Special Instructions.

**Useful For:** Confirming the autoimmune basis of a defect in neuromuscular transmission (eg, myasthenia gravis: MG, Lambert-Eaton syndrome: LES) Distinguishing LES from 2 recognized autoimmune forms of MG Raising the index of suspicion for cancer, particularly primary lung carcinoma (N-type calcium channel antibody) Providing a quantitative autoantibody baseline for future comparisons in monitoring a patient's clinical course and response to immunomodulatory treatment

**Interpretation:** A patient's autoantibody profile is more informative than the result of any single test for supporting a diagnosis of Myasthenia Gravis (MG) or Lambert-Eaton syndrome (LES), and for predicting the likelihood of lung carcinoma. Muscle acetylcholine receptor (AChR) and striational antibodies are characteristic but not diagnostic of MG. One or both are found in 13% of patients with LES, but calcium channel antibodies are not found in MG (with exception of rare non-thymomatous paraneoplastic cases). Muscle AChR binding antibody is found in 90% of nonimmunosuppressed MG patients who have thymoma, and 80% have a striational antibody. Calcium channel antibodies have not been encountered with thymoma. The likelihood of thymoma is greatest when striational antibody is accompanied by a high muscle AChR modulating antibody value (> or =90% AChR loss). Detection of CRMP-5-IgG also is consistent with thymoma in patients not at risk for lung carcinoma. N-type calcium channel antibodies are more highly associated with primary lung cancer than P/Q-type. One or all of the autoantibodies in the MG/LES evaluation can occur with neoplasia without evidence of neurological impairment. Calcium channel antibodies may disappear soon after commencing immunosuppressant therapy. Other serological markers of lung cancer also may disappear. One or both calcium channel antibodies (P/Q and N) can occur with paraneoplastic and idiopathic cerebellar ataxia, encephalomyeloneuropathies, and autonomic neuropathy. Titers are generally higher in patients with severe weakness, but severity cannot be predicted by antibody titer. AChR and striational antibodies may be undetectable for 6 to 12 months after MG symptom onset and similarly P/Q-type calcium channel antibody may be undetectable for 6 to 12 months after LES onset. Only about 5% of nonimmunosuppressed adult patients with generalized MG remain seronegative for muscle AChR and striational autoantibodies beyond 12 months. The alternative muscle autoantigen, MuSK, accounts for approximately 1/3 of seronegative MG cases with predominantly oculobulbar symptoms.
Reference Values:
ACh RECEPTOR (MUSCLE) BINDING ANTIBODY
< or =0.02 nmol/L

ACh RECEPTOR (MUSCLE) MODULATING ANTIBODIES
0-20% (reported as __% loss of AChR)

N-TYPE CALCIUM CHANNEL ANTIBODY
< or =0.03 nmol/L

P/Q-TYPE CALCIUM CHANNEL ANTIBODY
< or =0.02 nmol/L

STRIATIONAL (STRIATED MUSCLE) ANTIBODIES
<1:120


SGTF
35860

MYB (6q23) Rearrangement FISH, Tissue

Clinical Information: Salivary adenoid cystic carcinomas (ACC), although uncommon, are frequent among salivary gland malignancies. ACC is typically an aggressive tumor with a poor prognosis. Histologically, ACC show significant morphologic overlap with other salivary gland tumors, but have a much different clinical course. Because ACC requires a management distinct from histologically similar lesions, it is important to make an accurate diagnosis. Translocations between MYB (6q23.3) and NFIB (9p24) have been identified in a large proportion of primary salivary gland ACC. These alterations have not been identified in other salivary gland tumors. Therefore, separation of MYB, in the proper clinical and histologic context, is diagnostic for ACC and can be confirmed by FISH with MYB break-apart probes.

Useful For: Assessing for MYB gene rearrangements in patients with primary salivary gland carcinoma to aid in confirming or excluding the diagnosis of primary salivary gland adenoid cystic carcinomas

Interpretation: A positive result is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result suggests rearrangement of the MYB locus. The presence of a MYB rearrangement in conjunction with the proper clinical and histologic features is diagnostic of adenoid cystic carcinomas (ACC). A confirmed diagnosis of ACC results in specific clinical management that may be distinct from the management of other salivary gland neoplasms. A negative result suggests no rearrangement of the MYB gene region at 6q23.3. The absence of a MYB rearrangement does not exclude the diagnosis of ACC, as a subset of ACCs do not show an MYB rearrangement.

Reference Values:
An interpretive report will be provided.

MYC Immunostain, Technical Component Only

Clinical Information: MYC is a proto-oncogene commonly overexpressed in many malignant neoplasms, including some B-cell lymphomas. MYC translocations are a hallmark abnormality of Burkitt lymphoma. The presence of the MYC translocation may be a helpful indicator of poor prognosis or an aggressive clinical course in diffuse large B-cell lymphoma.

Useful For: Assessment of MYC expression

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Mycobacteria and Nocardia Culture

Clinical Information: Mycobacteria species are responsible for significant morbidity and mortality in both immunocompromised and immunocompetent hosts. Mycobacterium tuberculosis is the causative agent of tuberculosis and it kills nearly 2 million people in the world each year. Nontuberculous mycobacteria such as M avium complex and M abscessus cause a variety of infections (eg, respiratory, skin, and soft tissue) and are important to detect and correctly identify in order to aid in clinical decision making. There are more than 170 recognized species of mycobacteria and identification of these organisms to the species level is often required to help guide appropriate therapy. Although there are direct detection methods available for M tuberculosis, growth of the organism on culture media is still necessary to allow for antimicrobial susceptibility testing. At this time, direct molecular detection methods are lacking for the nontuberculous mycobacteria and growth in culture is critical for identification and antimicrobial susceptibility testing. Nocardia species and other aerobic actinomycetes (eg, Tsukamurella species, Gordonia species, Rhodococcus species) are also important causes of disease and isolation on culture media is important to facilitate identification and antimicrobial susceptibility testing. Nocardia and the other aerobic actinomycetes grow well on mycobacterial medium and, therefore, ordering a mycobacterial culture is recommended when infection with this group of organisms is suspected.

Useful For: Detection and identification of Mycobacterium species, Nocardia species, and other aerobic actinomycetes Identification is performed using the Hologic/GenProbe AccuProbes for selected Mycobacterium species, matrix assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry, or 500-base pair 16S rRNA gene sequencing M tuberculosis complex species identification can be done upon request using rapid PCR targeting the regions of difference (RD) genomic areas

Interpretation: A final negative report is issued after 42 days of incubation. Positive cultures are reported as soon as detected.
**Reference Values:**
Negative

**Clinical References:**

**ISMY**
45265

**Mycobacteria Ident by Sequencing (Bill Only)**

**Reference Values:**
This test is for billing purposes only. This is not an orderable test.

**CTBBL**
82443

**Mycobacterial Culture, Blood**

**Clinical Information:** Mycobacteremia occurs most often in immunocompromised hosts. The majority of disseminated mycobacterial infections are due to Mycobacterium avium complex but bacteremia can also be caused by other mycobacterial species including, but not limited to, Mycobacterium tuberculosis complex, Mycobacterium kansasi, Mycobacterium fortuitum, Mycobacterium chelonae, Mycobacterium scrofulaceum, Mycobacterium szulgai, and Mycobacterium xenopi. (1) Mycobacterial blood cultures may be indicated for patients presenting with signs and symptoms of sepsis, especially fever of unknown origin.

**Useful For:** Diagnosing mycobacteremia

**Interpretation:** A positive result may support the diagnosis of mycobacteremia.

**Reference Values:**
Negative
If positive, mycobacteria is identified.
A final negative report will be issued after 42 days of incubation.

**Clinical References:**

**MTBRP**
88807

**Mycobacterium tuberculosis Complex, Molecular Detection, PCR**

**Clinical Information:** Each year, Mycobacterium tuberculosis accounts for approximately 1.4 million deaths and is responsible for 9 million newly diagnosed cases of tuberculosis worldwide. M tuberculosis is spread from person-to-person via respiratory transmission, and has the potential to become resistant to many or all of the antibiotics currently used if antimycobacterial treatment is not promptly initiated. Therefore, rapid and accurate detection of M tuberculosis in patient specimens is of clinical and public health importance. Conventional culture methods can generally detect M tuberculosis in 2 to 3 weeks, although up to 8 weeks of incubation may be required in some instances. Developed at Mayo Clinic, this rapid PCR assay detects M tuberculosis complex DNA directly from respiratory specimens and other specimens without waiting for growth in culture and, therefore, the results are available the same day the specimen is received in the laboratory. A mycobacterial culture should always be performed in addition to the PCR assay. The PCR assay is rapid but the culture has increased sensitivity over the PCR assay. The PCR assay targets a unique sequence within the katG gene, which is present in members of the M tuberculosis complex. In addition, the assay can detect
genotypic resistance to isoniazid mediated by mutations in the katG target, when present.

**Useful For:** Rapid detection of Mycobacterium tuberculosis complex DNA, preferred method Detection of M tuberculosis, when used in conjunction with mycobacterial culture

**Interpretation:** A positive result indicates the presence of Mycobacterium tuberculosis complex DNA. Members of the M tuberculosis complex detected by this assay include M tuberculosis, M bovis, M bovis Bacillus Calmette-Guerin, M africanum, M canetti, and M microti. Other species within the M tuberculosis complex (eg, M caprae, M pinnipedii, and M mungi) should, in theory, be detected using the primer and probe sequences in this assay, but they have not been tested. This assay method does not distinguish between the species of the M tuberculosis complex. A negative result indicates the absence of detectable M tuberculosis complex DNA. Isoniazid (INH) resistance mediated through a katG mutation will be reported when observed but lack of a katG mutation does not imply that the isolate is susceptible to INH. There are other genetic loci in addition to katG that can contribute to resistance for this drug.

**Reference Values:**
Not applicable

**Clinical References:**

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**MTBT 62203**

**Mycobacterium tuberculosis Complex, Molecular Detection, PCR, Paraffin**

**Clinical Information:** Each year, Mycobacterium tuberculosis accounts for approximately 1.4 million deaths and is responsible for 9 million newly diagnosed cases of tuberculosis worldwide. M tuberculosis is spread from person-to-person via respiratory transmission, and has the potential to become resistant to many or all of the antibiotics currently used if antimycobacterial treatment is not promptly initiated. Therefore, rapid and accurate detection of M tuberculosis in patient specimens is of clinical and public health importance. Conventional culture methods can generally detect M tuberculosis in 2 to 3 weeks, although up to 8 weeks of incubation may be required in some instances. Developed at Mayo Clinic, this rapid PCR assay detects M tuberculosis complex DNA directly from respiratory specimens and other specimens without waiting for growth in culture and, therefore, the results are available the same day the specimen is received in the laboratory. A mycobacterial culture should always be performed in addition to the PCR assay. The PCR assay is rapid but the culture has increased sensitivity over the PCR assay. The PCR assay targets a unique sequence within the katG gene, which is present in members of the M tuberculosis complex. In addition, the assay can detect genotypic resistance to isoniazid mediated by mutations in the katG target, when present.

**Useful For:** Preferred method for rapid detection of Mycobacterium tuberculosis complex DNA in formalin-fixed, paraffin-embedded tissue specimens Detection of M tuberculosis complex

**Interpretation:** A positive result indicates the presence of Mycobacterium tuberculosis complex DNA. Members of the M tuberculosis complex detected by this assay include M tuberculosis, M bovis, M bovis Bacillus Calmette-Guerin, M africanum, M canetti, and M microti. The other species within the M tuberculosis complex (eg, M caprae, M pinnipedii, and M mungi) should, in theory, be detected using the primer and probe sequences in this assay, but they have not been tested at this time. This assay method does not distinguish between the species of the M tuberculosis complex. A negative result indicates the absence of detectable M tuberculosis complex DNA. Isoniazid (INH) resistance mediated through a katG mutation will be reported when observed but lack of a katG mutation does not imply that the isolate is susceptible to INH. There are other genetic loci in addition to katG that can contribute to resistance for this drug.

**Reference Values:**
Not applicable

**Clinical References:** 1. Iseman MD: A clinician’s guide to tuberculosis. Philadelphia, PA. Lippincott
**MTBPZ**

**Mycobacterium tuberculosis Complex, Pyrazinamide Resistance by pncA DNA Sequencing**

**Clinical Information:** The protein product of the Mycobacterium tuberculosis complex pncA gene is an enzyme that is responsible for activation of the prodrug pyrazinamide (PZA). DNA sequencing of the Mycobacterium tuberculosis complex pncA gene can be used to detect mutations that correlate with in vitro PZA resistance. The sequencing result can be available in as little as 1 day after the Mycobacterium tuberculosis complex isolate grows in culture, thereby providing a more rapid susceptibility result than the average 10 to 14 days required by phenotypic broth methods.

**Useful For:** Detection of genotypic resistance to pyrazinamide by Mycobacterium tuberculosis complex isolates

**Interpretation:** Polymorphisms in the pncA gene that have been previously correlated in our laboratory with pyrazinamide (PZA) resistance will be reported as "Mutation was detected in pncA suggesting resistance to pyrazinamide." Wild-type pncA or a silent pncA gene polymorphism (ie, no change in the amino acid translation) will be reported as "No mutation was detected in pncA." New polymorphisms in the pncA gene that have not previously been seen in our laboratory will require additional testing using a reference broth method to determine their correlation with PZA resistance.

**Reference Values:**
Pyrazinamide resistance not detected

**Clinical References:**

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**MPA**

**Mycophenolic Acid, Serum**

**Clinical Information:** Mycophenolate mofetil (CellCept) is a new immunosuppressive agent useful in organ transplantation. It is approved for use in renal, hepatic, and cardiac transplants. When mycophenolate mofetil enters the blood, it is immediately metabolized to the active drug, mycophenolic acid (MPA), which inhibits inosine monophosphate dehydrogenase and interferes with the de novo pathway of guanosine nucleotide synthesis selectively in lymphocytes. MPA inhibits proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific stimulation. MPA acts in the same fashion as azathioprine, and MPA is suggested as replacement therapy for azathioprine. The drug is deactivated by the hepatic enzyme, uridine diphosphate glucuronosyltransferase to form mycophenolic acid glucuronide (MPA-G). The principle clinical problem encountered in MPA therapy is excessive immunosuppression, which predisposes the patient to systemic infection. Measurement of the blood level of MPA and MPA-G can be useful to guide therapy. Monitoring is recommended immediately after transplant up to 3 weeks after therapy is initiated to evaluate dosing adequacy. Additional monitoring is indicated if the MPA level is not in the therapeutic range or if a major change in health status occurs.

**Useful For:** Monitoring therapy with CellCept to ensure adequate blood levels and avoid overimmunosuppression
**Interpretation:** Trough serum levels of mycophenolic acid (MPA) at steady-state (>2 weeks at the same dose) in the range of 1.0 to 3.5 mcg/mL indicate adequate therapy. Mycophenolic acid glucuronide (MPA-G) levels in the range of 35 to 100 mcg/mL indicate that the patient has normal uridine diphosphate glucuronosyltransferase (UGT) metabolic capacity. MPA-G levels are typically in the range of 100 to 250 mcg/mL during the 2 weeks following transplantation. MPA-G typically decreases after this initial post-transplant phase. Trough steady-state serum MPA levels >4.0 mcg/mL indicate that the patient is overimmunosuppressed and susceptible to systemic infections. Decreased dosages may be indicated in these cases. Low MPA levels and high MPA-G levels suggest that the patient has an active UGT metabolic capability; higher doses may be required to maintain therapeutic levels of MPA. Some patients have a high UGT metabolic capacity. These patients may require 1 gram or more 3 times a day to maintain trough serum MPA levels in the range of 1.0 mcg/mL to 3.5 mcg/mL. They are likely to have MPA-G levels >100 mcg/mL. MPA-G is inactive; MPA-G levels only describe the patient’s metabolic status. Patients who have low UGT conjugating capability may become overimmunosuppressed, indicated by a trough steady-state serum MPA level >4.0 mcg/mL and a MPA-G level <40 mcg/mL. Dose reduction or interval prolongation is indicated in this case.

**Reference Values:**

**MYCOPHENOLIC ACID (MPA)**
1.0-3.5 mcg/mL

**MPA GLUCURONIDE**
35-100 mcg/mL


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**Mycoïplasma genitalium, Molecular Detection, PCR**

**Clinical Information:** Mycoïplasma genitalium causes acute and chronic nongonococcal urethritis, cervicitis, and pelvic inflammatory disease. Culture isolation is technically challenging; PCR is the diagnostic test of choice.

**Useful For:** Rapid, sensitive, and specific identification of Mycoïplasma genitalium from genitourinary and reproductive sources

**Interpretation:** A positive PCR result for the presence of a specific sequence found within the Mycoïplasma genitalium tuf gene indicates the presence of M genitalium DNA in the specimen. A negative PCR result indicates the absence of detectable M genitalium DNA in the specimen, but does not rule-out infection as false-negative results may occur due to the following: inhibition of PCR, sequence variability underlying the primers or probes, or the presence of M genitalium in quantities below the limit of detection of the assay.

**Reference Values:** Not applicable


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**Mycoïplasma hominis, Molecular Detection, PCR**

**Clinical Information:** Mycoïplasma hominis has been associated with a number of clinically
significant infections, although it is also part of the normal genital flora. M hominis may be found in the respiratory specimens and spinal fluid of neonates. Although the clinical significance of such findings is often unclear, as spontaneous clinical recovery may occur without specific treatment, in premature infants, clinical manifestations of meningoencephalitis have been reported. M hominis may play a role in some cases of pelvic inflammatory disease, usually in combination with other organisms. M hominis may be isolated from amniotic fluid of women with preterm labor, premature rupture of membranes, spontaneous term labor, or chorioamnionitis; there is evidence that it may be involved in postpartum fever or fever following abortion, usually as a complication of endometritis. M hominis has rarely been associated with septic arthritis (including prosthetic joint infection), pyelonephritis, intraabdominal infection, wound infection, endocarditis, central nervous system infection (including meningoencephalitis, brain abscess, central nervous system shunt infection and subdural empyema), pneumonia, and infected pleural and pericardial effusions. Extragenital infection typically occurs in those with hypogammaglobulinemia or depressed cell-mediated immunity; in lung transplant recipients in particular, M hominis has been associated with pleuritis and mediastinitis. Recent evidence implicates donor transmission in some cases of M hominis infection in lung transplant recipients. PCR detection of M hominis is sensitive, specific, and provides same-day results. Although this organism can occasionally be detected in routine plate cultures, this is neither a rapid nor a sensitive approach to detection. Specialized cultures are more time consuming than the described PCR assay. The described PCR assay has replaced conventional culture for M hominis at Mayo Medical Laboratories due to its speed and equivalent performance to culture.

**Useful For:** Rapid, sensitive, and specific identification of Mycoplasma hominis from synovial fluid, genitourinary, reproductive, lower respiratory sources, pleural/cheat fluid, pericardial fluid, and wound specimens

**Interpretation:** A positive PCR result for the presence of a specific sequence found within the Mycoplasma hominis tuf gene indicates the presence of M hominis DNA in the specimen. A negative PCR result indicates the absence of detectable M hominis DNA in the specimen, but does not rule-out infection as falsely negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of M hominis in quantities less than the limit of detection of the assay.

**Reference Values:** Not applicable

**Clinical References:**


**Mycoplasma hominis, Molecular Detection, PCR, Blood**

**Clinical Information:** Mycoplasma hominis has been associated with a number of clinically significant infections, although it is also part of the normal genital flora. M hominis may be found in the respiratory specimens and spinal fluid of neonates. Although the clinical significance of such findings is often unclear, as spontaneous clinical recovery may occur without specific treatment, in premature infants clinical manifestations of meningoencephalitis have been reported. M hominis may play a role in some cases of pelvic inflammatory disease, usually in combination with other organisms. M hominis may be isolated from amniotic fluid of women with preterm labor, premature rupture of membranes, spontaneous term labor, or chorioamnionitis; there is evidence that it may be involved in postpartum fever or fever following abortion, usually as a complication of endometritis. M hominis has rarely been associated with septic arthritis (including prosthetic joint infection), pyelonephritis, intraabdominal infection, wound infection, endocarditis, central nervous system infection (including meningoencephalitis, brain abscess, central nervous system shunt infection and subdural empyema), pneumonia, and infected pleural and pericardial effusions. Extragenital infection typically occurs in those with hypogammaglobulinemia or depressed cell-mediated immunity; in lung transplant recipients in particular, M hominis has been associated with pleuritis and mediastinitis. Recent evidence
implicates donor transmission in some cases of M hominis infection in lung transplant recipients.

**Useful For:** Rapid, sensitive, and specific identification of Mycoplasma hominis from whole blood

**Interpretation:** A positive PCR result for the presence of a specific sequence found within the Mycoplasma hominis tuf gene indicates the presence of M hominis DNA in the specimen. A negative PCR result indicates the absence of detectable M hominis DNA in the specimen, but does not rule-out infection as falsely negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of M hominis in quantities less than the limit of detection of the assay.

**Reference Values:**
Not applicable

**Clinical References:**
Mycoplasma pneumoniae Antibodies, IgG and IgM, Serum

Clinical Information: Mycoplasma pneumoniae is a small bacterium transmitted via organism-containing droplets. It is a cause of upper respiratory infection, pharyngitis, and tracheobronchitis, particularly in children, and has been associated with approximately 20% of cases of community-acquired pneumonia. Central nervous system and cardiac manifestations are probably the most frequent extrapulmonary complications of infections due to M pneumoniae. The disease is usually self-limited, although severe disease has been reported in immunocompromised patients. Identification of M pneumoniae by culture-based methods is time consuming and insensitive. Serology-based assays for M pneumoniae have several drawbacks. The development of IgM antibodies takes approximately 1 week and the IgM response in adults may be variable or it may be decreased in immunosuppressed individuals. Confirmation of the disease is dependent on the observation of a 4-fold rise in IgG antibody titers between acute and convalescent specimens, several weeks following the initial onset of illness, providing clinical utility only for retrospective testing. Real-time PCR offers a rapid and sensitive option for detection of M pneumoniae DNA from clinical specimens allows for diagnosis of acute or current infection.

Useful For: Screening for recent or past exposure to Mycoplasma pneumoniae

Interpretation: IgG ELISA Result IgM ELISA Result Interpretation Positive Negative Results suggest past exposure. Positive Reactive Prior exposure to M pneumoniae detected. Confirmatory testing for IgM to M pneumonia will be performed by an immunofluorescence assay. Equivocal Negative Negative No antibodies to M pneumonia detected. Acute infection cannot be ruled out as antibody levels may be below the limit of detection. If clinically indicated, a second serum should be submitted in 14 to 21 days. Negative Reactive No prior exposure to Mycoplasma pneumoniae. Confirmatory testing for IgM to M pneumonia will be performed by an immunofluorescence assay. Equivocal Equivocal Negative Recommend follow-up testing in 10 to 14 days if clinically indicated. Reactive Confirmatory testing for IgM to M pneumonia will be performed by an immunofluorescence assay. Equivocal

Reference Values:
IgG: negative
IgM: negative
IgM by IFA: negative


Mycoplasma pneumoniae Antibodies, IgG, Serum

Clinical Information: Mycoplasma pneumoniae is an important respiratory tract pathogen. Several syndromes have been associated with the infection including pharyngitis, tracheobronchitis, pneumonia, and inflammation of the tympanic membrane presenting as bullous myringitis. M pneumoniae accounts for approximately 20% of all cases of pneumonia. Classically, it causes a disease that has been described as primary atypical pneumonia. The disease is of insidious onset with fever, headache, and malaise for 2 to 4 days before the onset of respiratory symptoms. Most cases do not require hospitalization. Symptomatic infections attributable to this organism most commonly occur in children and young adults (ages 2-19 years).

Useful For: Screen for recent or past exposure to Mycoplasma pneumoniae

Interpretation: A single positive IgG result only indicates previous immunologic exposure. Negative results do not rule out the presence of acute or ongoing Mycoplasma pneumoniae-associated disease. The specimen may have been drawn before the appearance of detectable antibodies. If testing is performed too early following primary infection, IgG may not be detectable. If a Mycoplasma infection
is clinically suspected, a second, convalescent specimen should be submitted in 14 to 21 days.

**Reference Values:**
Only orderable as part of a profile. For more information see MYCO / Mycoplasma pneumoniae Antibodies, IgG and IgM, Serum.

Negative

**Clinical References:** Smith T: Mycoplasma pneumoniae infections: diagnosis based on immunofluorescence titer of IgG and IgM antibodies. Mayo Clin Proc 1986;61:830-831

**MYCOM 48318**

**Mycoplasma pneumoniae Antibodies, IgM, Serum**

**Clinical Information:** Mycoplasma pneumoniae is an important respiratory tract pathogen. Several syndromes have been associated with the infection including pharyngitis, tracheobronchitis, pneumonia, and inflammation of the tympanic membrane presenting as bullous myringitis. M pneumoniae accounts for approximately 20% of all cases of pneumonia. Classically, it causes a disease that has been described as primary atypical pneumonia. The disease is of insidious onset with fever, headache, and malaise for 2 to 4 days before the onset of respiratory symptoms. Most cases do not require hospitalization. Symptomatic infections attributable to this organism most commonly occur in children and young adults (ages 2-19 years).

**Useful For:** Screen for recent or past exposure to Mycoplasma pneumoniae

**Interpretation:** Positive IgM results are consistent with recent infection, although false-positives may occur (see Cautions). Negative results do not rule out the presence of acute or ongoing Mycoplasma pneumoniae-associated disease. The specimen may have been drawn before the appearance of detectable antibodies. If testing is performed too early following primary infection, IgM may not be detectable. If a Mycoplasma infection is clinically suspected, a second, convalescent specimen should be submitted in 14 to 21 days.

**Reference Values:**
Only orderable as part of a profile. For more information see MYCO / Mycoplasma pneumoniae Antibodies, IgG and IgM, Serum.

Negative

**Clinical References:** Smith T: Mycoplasma pneumoniae infections: diagnosis based on immunofluorescence titer of IgG and IgM antibodies. Mayo Clin Proc 1986;61:830-831

**MYCON 48319**

**Mycoplasma pneumoniae Antibody Interpretation**

**Reference Values:**
Only orderable as part of a profile. For more information see MYCO / Mycoplasma pneumoniae Antibodies, IgG and IgM, Serum.

**FMPAB 90055**

**Mycoplasma pneumoniae Antibody, CF (CSF)**

**Reference Values:**
REFERENCE RANGE: <1:1

**Interpretive Criteria:**
<1:1 Antibody Not Detected
> or = 1:1 Antibody Detected

Diagnosis of infections of the central nervous system is accomplished by demonstrating the presence of
intrathecally-produced specific antibody. Interpretation of results may be complicated by low antibody levels found in CSF, passive transfer of antibody from blood, and contamination via bloody taps. The interpretation of CSF results must consider CSF-serum antibody ratios for the infectious agent.

**FMYPN**

Mycoplasma pneumoniae IgA

**Reference Values:**

Reference Ranges Mycoplasma IgA:

- 0 - 9 BU/mL
  - None Detected
  - There is no indication of M. pneumoniae infection.

- 10 - 20 BU/mL
  - Equivocal
  - Test a second sample, drawn two to four weeks later in parallel with the first sample. When second sample is equivocal the result should be considered as negative.

- 21 BU/mL and greater
  - Relevant detectable levels of IgA antibodies. Suggestive of current or chronic M. pneumoniae infection.

**MPRP**

Mycoplasma pneumoniae, Molecular Detection, PCR

**Clinical Information:** Mycoplasma pneumoniae is a small bacterium transmitted via organism-containing droplets. It is a cause of upper respiratory infection, pharyngitis, and tracheobronchitis, particularly in children, and has been associated with approximately 20% of cases of community acquired pneumonia.(1) Central nervous system and cardiac manifestations are probably the most frequent extrapulmonary complications of infections due to M pneumoniae. The disease is usually self-limited although severe disease has been reported in immunocompromised patients.(2) Identification of M pneumoniae by culture-based methods is time consuming and insensitive. Serology based assays for M pneumoniae have several drawbacks. The development of IgM antibodies takes approximately 1 week and the IgM response in adults may be variable or it may be decreased in immunosuppressed individuals.(3,4) Confirmation of the disease may be dependent on the observation of a 4-fold rise in IgG antibody titers between acute and convalescent specimens, several weeks following the initial onset of illness, providing clinical utility only for retrospective testing.(4) Real-time PCR offers a rapid and sensitive option for detection of M pneumoniae DNA from clinical specimens.

**Useful For:** Diagnosis of infections due to Mycoplasma pneumoniae

**Interpretation:** A positive result indicates the presence of Mycoplasma pneumoniae. A negative result does not rule out the presence of M pneumoniae and may be due to the presence of inhibitors within the specimen matrix, or the presence of organisms at numbers below the limits of detection of the assay.

**Reference Values:**

Not applicable

**Clinical References:**

**MYD88 Reflex to CXCR4 Mutation Detection**

**Clinical Information:** Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia (LPL/WM) is a B-cell lymphoma that is characterized by an aberrant accumulation of malignant lymphoplasmacytic cells in the bone marrow, lymph nodes and spleen. It is a B-cell neoplasm that can exhibit excess production of serum immunoglobulin-M symptoms related to hyper viscosity, tissue filtration, and autoimmune-related pathology. CXCR4 mutations are identified in approximately 30% to 40% of LPL/WM and are almost always in association with MYD88 L265P, which is highly prevalent in this neoplasm. The status of CXCR4 mutations in the context of MYD88 L265P is clinically relevant as important determinants of clinical presentation, overall survival, and therapeutic response to ibrutinib: A MYD88-L265P/CXCR4-WHIM (C-terminus nonsense/frameshift mutations) molecular signature is associated with intermediate to high bone marrow disease burden and serum IgM levels, less adenopathy, and intermediate response to ibrutinib in previously treated patients, a MYD88-L265P/CXCR4-WT (wild type) molecular signature is associated with intermediate bone marrow disease burden and serum IgM levels, more adenopathy, and highest response to ibrutinib in previously treated patients, and the MYD88-WT/CXCR4-WT molecular signature is associated with inferior overall survival, lower response to ibrutinib therapy in previously treated patients, and lower bone marrow disease burden in comparison to those harboring a MYD88-L265 mutation. This test is used to aid in the prognostication and therapeutic management of LPL/WM.

**Useful For:** The prognostication and clinical management of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia

**Interpretation:** Mutations detected or not detected. An interpretive report will be issued under the LPLFX / Reflexive Testing of MYD88 and CXCR4.

**Reference Values:**

An interpretive report will be provided

**Clinical References:**


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**MYD88, L265P, Somatic Gene Mutation, DNA Allele-Specific PCR**

**Clinical Information:** Single point mutation in MYD88 L265P is present in 67% to 100% of patients with lymphoplasmacytic lymphoma and these patients typically have clinical manifestations of Waldenstrom macroglobulinemia (often designated LPL/WM).

**Useful For:** Establishing the diagnosis of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia and helping to distinguish this low-grade B-cell lymphoma from other subtypes
**Interpretation:** Mutation present or not detected; an interpretive report will be issued.

**Reference Values:**
Mutation present or absent based on expected mutant PCR product size. Concurrent amplification of wild type MYD88 fragment determined for sample amplification integrity. MYD88 gene (NCBI accession NM_002468.4).

**Clinical References:**

**FMGA 57249**

**Myelin Assoc. Glycoprotein (MAG) Antibody w/Reflex to MAG-SGPG & MAG, EIA**

**Clinical Information:** MAG. Western Blot with reflexes is useful in detecting antibodies associated with autoimmune peripheral neuropathy.

**Reference Values:**
MAG Ab (IgM), Western Blot

Reference Range: Negative

MAG-SGPG Ab (IgM), EIA

Reference Range: 
< or = 1:1600

MAG Ab (IgM), EIA

<1:1600

Reference ranges for MAG IgM Antibody:

- Normal: <1:1600
- Moderately Elevated: 1:1600-1:3200
- Highly Elevated: >1:6400

**MOGFS 65563**

**Myelin Oligodendrocyte Glycoprotein (MOG-IgG1) Fluorescence-Activated Cell Sorting (FACS) Assay, Serum**

**Clinical Information:** Neuromyelitis optica (NMO), sometimes called Devic disease or opticospinal multiple sclerosis (MS) is a severe, relapsing, autoimmune, inflammatory and demyelinating central nervous system disease (IDD) that predominantly affects optic nerves and spinal cord.(1) The disorder is now recognized as a spectrum of autoimmunity (termed NMO spectrum disorders: NMOSD).(1-3) Brain lesions are observed in more than 60% of patients with NMOSD and approximately 10% will be MS-like.(4) Children tend to have greater brain involvement than adults, and brain lesions are more symptomatic than is typical for adult patients.(3) The clinical course is
characterized by relapses of optic neuritis or transverse myelitis, or both. Some patients may present with acute disseminated encephalomyelitis (ADEM). Many patients with NMOSD are misdiagnosed as having MS. More effective treatments combined with earlier and more accurate diagnosis has led to improved outcomes. Approximately 80% of patients with NMO are seropositive for aquaporin-4 (AQP4)-IgG.(5-7) In the remaining 20% of patients, myelin oligodendrocyte glycoprotein (MOG)-IgG is detected in up to a third.(8) The pathogenic target for the remaining patients remains unknown.

Detection of MOG-IgG is diagnostic of central nervous system (CNS) inflammatory demyelination, where the clinical phenotype (NMOSD, optic neuritis, transverse myelitis, ADEM) may be similar, but the immunopathology (astrocytopathy vs oligodendrocytopathy) and clinical outcome (worse vs better) is different.(9) Detection of MOG-IgG also predicts relapse.(10) More importantly, however, is that MOG-IgG seropositive IDDs are distinct from MS and treated differently.(8, 9) Treatments for IDDs seropositive for MOG-IgG include corticosteroids and plasmapheresis for acute attacks and mycophenolate mofetil, azathioprine, and rituximab for relapse prevention. Disease modifying agents, treatments promoted for MS, have been reported to exacerbate MOG-IgG1 seropositive IDDS. Therefore, early diagnosis and initiation of appropriate immunosuppressant treatment is important to optimize the clinical outcome by preventing further attacks. In 2015, Waters and colleagues (11) from Oxford University established a novel cell based assay for the measurement of IgG1 MOG antibodies based on previous findings that MOG antibodies are almost exclusively of the IgG1 subclass. They showed that their MOG-IgG1 flow cytometry assay eliminated false positives without losing true positives with low titers. The detection of MOG-IgG1 allowed non MS demyelinating diseases (ADEM, AQP4-IgG negative neuromyelitis optica spectrum disorder: including ON, TM) to be distinguished from MS.(12) Using a similar assay to our MOG-IgG1 flow cytometry assay, demonstrated high specificity of their MOG-IgG1 assay in which 49 patients with MS, 13 healthy control sera, and 37 AQP4-seropositive serum samples were all negative at a dilution of 1:20. Of 58 patients fulfilling 2006 Wingerchuk criteria for NMO, 21 (36%) tested negative for AQP4-IgG MOG-IgG1 was detected by cell based assay in 8 (38%) of these cases.(13) Testing of 1,109 consecutive sera sent for AQP4-IgG testing.(12) revealed 40 AQP4-IgG and 65 MOG-IgG1 positive cases. None were positive for both. The clinical diagnoses obtained in 33 MOG-IgG1 positive patients included 4 NMO, 1 ADEM and 11 optic neuritis (n = 11). All 7 patients with probable MS were MOG-IgG1 negative. This study provides Class II evidence that the presence of serum MOG-IgG1 distinguishes non-MS central nervous system (CNS) demyelinating disorders from MS (sensitivity 24%, 95% confidence interval [CI] 9%-45%; specificity 100%, 95% CI 88%-100%). The assay validated here, was developed using the MOG construct provided by Dr Waters(11) and the validation was based on a blinded comparison with the Oxford assay. Comparison was also made with the Euroimmun fixed cell based kit assay.(14) A recent longitudinal analysis with 2 year follow-up suggested that persistence of MOG-IgG is associated with relapses thus warranting relapse preventing.(10) Detection of MOG-IgG1 allows distinction from MS and is generally indicative of a relapsing disease, mandating initiation of immunosuppression, even after the first attack in some, thereby reducing attack frequency and disability in the future.

**Useful For:**

- Diagnosis of inflammatory demyelinating diseases (IDD) with similar phenotype to neuromyelitis optica spectrum disorder (NMOSD), including optic neuritis (single or bilateral) and transverse myelitis
- Diagnosis of autoimmune myelin oligodendrocyte glycoprotein (MOG)-opathy
- Diagnosis of neuromyelitis optica (NMO) Distinguishing NMOSD, acute disseminated encephalomyelitis (ADEM), optic neuritis, and transverse myelitis from multiple sclerosis early in the course of disease
- **Diagnosis of ADEM** Prediction of a relapsing disease course

**Interpretation:**

- A positive value for myelin oligodendrocyte glycoprotein (MOG)-IgG is consistent with an neuromyelitis optica (NMO)-like phenotype, and in the setting of acute disseminated encephalomyelitis (ADEM), optic neuritis and transverse myelitis indicates an autoimmune oligodendroglialopathy with potential for relapsing course. Identification of MOG-IgG allows distinction from MS and may justify initiation of appropriate immunosuppressive therapy (not MS disease-modifying agents) at the earliest possible time. This allows early initiation and maintenance of optimal therapy. Recommend follow-up in 3 to 6 months as persistence of MOG-IgG seropositivity predicts a relapsing course. This autoantibody is not found in healthy subjects.

**Reference Values:**

- Negative

**Clinical References:**


Myelodysplastic Syndrome (MDS), FISH

Clinical Information: Myelodysplastic syndromes (MDS) primarily occur in the older adult population and have a yearly incidence of 30 in 100,000 in persons greater than 70 years of age. These disorders are typically associated with a hypercellular bone marrow and low peripheral blood counts, and with significant morbidity and mortality. The eventual clinical outcome for patients with MDS relates to either bone marrow failure or transformation to acute myeloid leukemia. MDS can be either primary (de novo) or secondary (due to previous treatment with alkylating or etoposide chemotherapy, with or without radiation). Cytogenetic studies can provide confirmatory evidence of clonality in MDS and can be used to provide clinical prognostic or diagnostic information. Clonal cytogenetic abnormalities are more frequently observed in cases of secondary MDS (80% of patients) than in primary MDS (40%-60% of patients). The common chromosomal abnormalities associated with MDS include: inv(3), -5/5q-, -7/7q-, +8, 13q-, and 20q-. These abnormalities can be observed singly or in concert. In addition, MLL (KMT2A) rearrangements, t(1;3) and t(3;21) are more frequently associated with secondary MDS. Conventional chromosome analysis is the gold standard for identification of the common, recurrent chromosome abnormalities in MDS, however, some of the subtle rearrangements can be missed (eg, MLL and NUP98 abnormalities).

Useful For: Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with myelodysplastic syndromes or other myeloid malignancies. Evaluating specimens in which standard cytogenetic analysis is unsuccessful. Identifying and tracking known chromosome abnormalities in patients with myeloid malignancies and tracking response to therapy.

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values: An interpretive report will be provided.

Myelodysplastic Syndrome by Flow Cytometry, Bone Marrow

Clinical Information: Myelodysplastic syndromes (MDS) encompass a heterogeneous group of clonal hematopoietic neoplasms characterized by cytopenias due to ineffective hematopoiesis, variable degrees of dysmyelopoietic morphologic features, and increased risks of evolution to acute myeloid leukemia. Per 2008 World Health Organization recommendations, a definitive diagnosis of MDS requires identification of 1 or more of the following findings: clear-cut morphologic features of dysplasia in greater than or equal to 10% of the cells in 1 or more of the 3 hematopoietic lineages; increased (but <20%) blood or marrow blasts with or without Auer rods; and well-characterized clonal cytogenetic abnormalities.(3-4) However, at present, in approximately 50% of MDS patients, no informative or diagnostic clonal cytogenetic abnormalities are identified. Not infrequently, morphologic review of the patient's blood and marrow specimen is inconclusive. And yet it is important to distinguish MDS and other clonal myeloid neoplasms from other nonmalignant and nonneoplastic possibilities in the differential diagnosis such as medication effects or other toxic exposures, copper deficiency, infections, and left-shifted hematopoietic regeneration, among others. In such settings, when used in conjunction with appropriate clinical and morphologic findings, flow cytometry immunophenotyping analysis can provide additional diagnostic information to help distinguish an underlying clonal hematopoietic neoplasm from a reactive or secondary response.(2,5)

Useful For:
- Detecting increased blasts
- Characterizing blast phenotypes
- Identifying abnormal patterns of myeloid maturation as seen in myelodysplastic syndromes and other clonal myeloid neoplasms
- Providing additional adjunct diagnostic information in cases with equivocal or suspicious morphologic features for myelodysplastic syndrome (MDS), MDS/myeloproliferative neoplasms including chronic myelomonocytic leukemia, and other clonal myeloid neoplasms

Interpretation: The final interpretation integrates 1) the quantity of blasts; 2) blast phenotype with respect to CD13/HLA-DR expression and/or abnormal coexpression of CD2, CD7, and/or CD56; and 3) myeloid maturation patterns based on CD13/CD16 plot. In combination, the total number of abnormalities detected and the distinctiveness of the abnormalities themselves help determine the likelihood of specimen involvement by a clonal myeloid neoplasm.

Reference Values:
An interpretive report will be provided. This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and, if available, morphologic features will be provided by a board-certified hematopathologist for every case.

Clinical References:

Myeloid Sarcoma, FISH, Tissue

Clinical Information: Myeloid sarcomas are tumors made up of myeloblasts or immature myeloid cells that occur in extramedullary sites or in bone. They can occur concurrently with acute or chronic myeloid leukemia (AML or CML) or may precede the leukemia or other myeloid neoplasms. They may also be the initial manifestation of relapse of a previously treated primary AML in remission. Due to this
extramedullary presentation, the bone marrow may have a low number of myeloblasts due to a lack of bone marrow involvement. The most common abnormalities seen in myeloid sarcomas are fusion of RUNX1/T1/RUNX1 (t[8;21][q22;q22]), PML/RARA (t[15;17][q24;q21]), BCR/ABL1 (t[9;22][q34;q11.2]), inversion of MYH11/CBF (inv[16][q13.1q22]), and rearrangements of MLL (KMT2A; t[11q23;var]). In general, AML patients with an inv(16), t(8;21), t(9;22), or t(15;17) have a favorable prognosis, while AML patients with a rearrangement of t(11q23) have an unfavorable prognosis. Thus, the detection of these abnormalities in an extramedullary presentation of AML can be prognostically important.

Useful For: Supporting the diagnosis of myeloid sarcoma when coordinated with a surgical pathology consultation

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for a given probe set. A positive result supports the diagnosis of a myeloid sarcoma. A negative result does not exclude the diagnosis of a myeloid sarcoma.

Reference Values:
An interpretive report will be provided.


Myeloma, FISH, Fixed Cells

Clinical Information: Multiple myeloma is a hematologic neoplasm that generally originates in the bone marrow and develops from malignant plasma cells. There are 4 main categories of myeloma: asymptomatic myeloma, smoldering myeloma, indolent myeloma, and multiple myeloma. Asymptomatic myeloma patients have nonspecific symptoms that may be attributed to other diseases. Generalized bone pain, anemia, numbness or limb weakness, symptoms of hypercalcemia, and recurrent infections are all symptoms that may indicate myeloma. In smoldering myeloma there is a monoclonal protein spike, but it is stable. Indolent myeloma is a slowly progressing myeloma. As myeloma progresses, the malignant plasma cells interfere with normal blood product formation in the bone marrow resulting in anemia and leukopenia. Myeloma also causes an overstimulation of osteoclasts, causing excessive breakdown of bone tissue without the normal corresponding bone formation. These bone lesions are seen in approximately 66% of myeloma patients. In advanced disease, bone loss may reach a degree where the patient suffers fractures easily. Multiple myeloma is increasingly recognized as a disease characterized by marked cytogenetic, molecular, and proliferative heterogeneity. This heterogeneity is manifested clinically by varying degrees of disease aggressiveness. Multiple myeloma patients with more aggressive disease experience suboptimal responses to some therapeutic approaches; therefore, identifying these patients is critically important for selecting appropriate treatment options.

Useful For: Aiding in the diagnosis of new cases of multiple myeloma Identifying prognostic markers based on the abnormalities found

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe.

Reference Values:
An interpretive report will be provided.


### Myeloperoxidase (MPO) Immunostain, Technical Component Only

**Clinical Information:** Myeloperoxidase shows strong cytoplasmic immunoreactivity in neutrophilic and eosinophilic granulocytes and their precursors. Virtually all other cell types are negative for myeloperoxidase staining. Antibodies to myeloperoxidase are most useful diagnostically to support myeloid lineage in acute leukemias. These antibodies also facilitate the detection of granulocyte precursors in myeloproliferative disorders and myelodysplastic syndromes.

**Useful For:** A marker of myeloid lineage

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

### Myeloperoxidase Antibodies, IgG, Serum

**Clinical Information:** Myeloperoxidase (MPO) enzyme is found in neutrophil primary granules and monocyte lysosomes. MPO catalyzes the conversion of hydrogen peroxide to hypochlorite and hypochlorous acid. MPO is encoded by a single gene that undergoes posttranslational modification to produce the active enzyme found in leukocytes. Autoantibodies to MPO (MPO antineutrophil cytoplasmic antibodies: ANCA) occur in several diseases and may be involved in the pathogenesis of vascular inflammation in patients with microscopic polyangiitis (MPA).(1,2) Patients with MPA often develop MPO ANCA and may present with azotemia secondary to glomerulonephritis (pauci-immune necrotizing glomerulonephritis). MPO ANCA are not specific for MPA, and also may be detected in patients with systemic lupus erythematosus with or without lupus nephritis, Goodpasture syndrome and Churg-Strauss syndrome. Lupus nephritis and Goodpasture syndrome, as well as Wegener granulomatosis may present with azotemia and progressive renal failure. It is not possible to distinguish among these diseases on the basis of clinical signs and symptoms; autoantibody testing may be helpful.

**Useful For:** Evaluating patients suspected of having immune-mediated vasculitis, especially microscopic polyangiitis (MPA), when used in conjunction with other autoantibody tests (see Cautions) May be useful to follow treatment response or to monitor disease activity in patients with MPA

**Interpretation:** A positive result has a high predictive value for microscopic polyangiitis (MPA) in
patients with negative test results for systemic lupus erythematosus (antinuclear antibodies) and Goodpasture syndrome (glomerular basement membrane antibody). A negative result significantly diminishes the likelihood that a patient has MPA. While myeloperoxidase levels often decline following successful treatment of MPA, specific guidelines for this clinical purpose are not available.

**Reference Values:**

- <0.4 U (negative)
- 0.4-0.9 U (equivocal)
- >1.0 U (positive)

Reference values apply to all ages.

**Clinical References:**


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**Myeloproliferative Neoplasm (MPN), CALR with Reflex to MPL**

**Clinical Information:** JAK2 V617F mutation is present in 95% to 98% of polycythemia vera (PV), and 50% to 60% of primary myelofibrosis (PMF) and essential thrombocythemia (ET). Detection of the JAK2 V617F is useful to help establish the diagnosis of a myeloproliferative neoplasm (MPN). However, a negative JAK2 V617F result does not indicate the absence of MPN. Other important molecular markers in BCR-ABL1-negative MPN include CALR exon 9 mutations (20%-30% of PMF and ET) and MPL exon 10 mutations (5%-10% of PMF and 3%-5% of ET). Mutations in JAK2, CALR, and MPL are essentially mutually exclusive. A CALR mutation is associated with decreased risk of thrombosis in both ET and PMF, and confers a favorable clinical outcome in PMF patients. A triple negative (JAK2 V617F, CALR, and MPL-negative) genotype is considered a high-risk molecular signature in PMF.

**Useful For:** Aiding in the distinction between a reactive cytosis and a myeloproliferative neoplasm when JAK2V617F testing result is negative

**Interpretation:** The results will be reported as 1 of the 3 following states: -Positive for CALR mutation -Positive for MPL mutation -Negative for CALR and MPL mutations Positive mutation status is highly suggestive of a myeloid neoplasm and clinicopathologic correlation is necessary in all cases. Negative mutation status does not exclude the presence of a myeloproliferative neoplasm or other neoplasms.

**Reference Values:**

An interpretive report will be provided.

**Clinical References:**

to CALR and MPL

**Clinical Information:** The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. BCR-ABL1-negative myeloproliferative neoplasms (MPN) frequently harbor an acquired single nucleotide mutation in JAK2 characterized as c.G1849T; p. Val617Phe (V617F). The JAK2 V617F is present in 95% to 98% of polycythemia vera (PV), and 50% to 60% of primary myelofibrosis (PMF) and essential thrombocythemia (ET). It has also been described infrequently in other myeloid neoplasms, including chronic myelomonocytic leukemia and myelodysplastic syndrome. Detection of the JAK2 V617F is useful to help establish the diagnosis of MPN. However, a negative JAK2 V617F result does not indicate the absence of MPN. Other important molecular markers in BCR-ABL1-negative MPN include CALR exon 9 mutation (20%-30% of PMF and ET) and MPL exon 10 mutation (5%-10% of PMF and 3%-5% of ET). Mutations in JAK2, CALR, and MPL are essentially mutually exclusive. A CALR mutation is associated with decreased risk of thrombosis in both ET and PMF, and confers a favorable clinical outcome in PMF patients. A triple negative (JAK2 V617F, CALR, and MPL-negative) genotype is considered a high-risk molecular signature in PMF.

**Useful For:** Aiding in the distinction between a reactive cytosis and a chronic myeloproliferative disorder Evaluating for mutations in JAK2, CALR, and MPL in an algorithmic process

**Interpretation:** The results will be reported as 1 of the 4 following states: -Positive for JAK2 V617F mutation -Positive for CALR mutation -Positive for MPL mutation -Negative for JAK2 V617F, CALR, and MPL mutations Positive mutation status is highly suggestive of a myeloid neoplasm, but must be correlated with clinical and other laboratory features for definitive diagnosis. Negative mutation status does not exclude the presence of a myeloproliferative neoplasm or other neoplasms. Results below the laboratory cutoff for positivity are of unclear clinical significance at this time.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**MCA 9746 Myocardial Antibodies, Serum**

**Clinical Information:** Myocardial antibodies occur in the sera of patients who have acute rheumatic fever and carditis, or who have sustained mechanical (surgical or traumatic) or ischemic damage to myocardial tissue in the postcardiotomy and post myocardial infarction syndromes. In the "myocardial injury" syndromes, circulating myocardial antibodies become detectable 2 to 3 weeks after the injury in 30% (infarction) to 70% (postsurgical) of cases and remain detectable for 3 to 8 weeks. Myocardial antibodies have been detected in some patients with idiopathic cardiomyopathy. The pathogenic
The significance of myocardial antibodies is not known.

**Useful For:** Evaluating patients suspected of having post cardiotomy or post myocardial infarction syndromes Evaluating patients suspected of having inflammatory cardiomyopathy

**Interpretation:** Elevated in 30% of myocardial injury patients by the 2nd or 3rd week

**Reference Values:**
- Negative
- If positive, results are titered.
- Reference values apply to all ages.


### Myocarditis/Pericarditis Panel

**Reference Values:**

**MYOCARDITIS-PERICARDITIS PANEL**

**COXSAKIE B(1-6) ANTIBODIES, SERUM**

**REFERENCE RANGE:** <1:8

**INTERPRETIVE CRITERIA:**
- <1:8 Antibody Not Detected
- ≥ 1:8 Antibody Detected

Single titers of ≥ 1:32 are indicative of recent infection. Titers of 1:8 or 1:16 may be indicative of either past or recent infection, since CF antibody levels persist for only a few months. A four-fold or greater increase in titer between acute and convalescent specimens confirms the diagnosis. There is considerable crossreactivity among enteroviruses; however, the highest titer is usually associated with the infecting serotype.

This test was developed and its performance characteristics have been determined by Quest Diagnostics Infectious Disease. It has not been cleared or approved by FDA. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

**ECHOVIRUS ANTIBODIES, SERUM**

**REFERENCE RANGE:** <1:8

**INTERPRETIVE CRITERIA:**
- <1:8 Antibody Not Detected
- ≥ 1:8 Antibody Detected

Single titers ≥ 1:32 are indicative of recent infection. Titers of 1:8 and 1:16 may be indicative of either past or recent infection, since CF antibody levels persist for only a few months. A four-fold or greater increase in titer between acute and convalescent specimens confirms the diagnosis. There is considerable crossreactivity among enteroviruses; however, the highest titer is usually associated with the infecting serotype.

This test was developed and its performance characteristics have been determined by Quest Diagnostics Infectious Disease. It has not been cleared or approved by FDA. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

**INFLUENZA TYPES A AND B ANTIBODIES, SERUM**

Current as of October 11, 2018 2:20 pm CDT   800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
REFERENCE RANGE: <1:8

INTERPRETIVE CRITERIA:
<1:8 Antibody Not Detected
> or = 1:8 Antibody Detected

Single titers of > or = 1:64 are indicative of recent infection. Titers of 1:8 to 1:32 may be indicative of either past or recent infection, since CF antibody levels persist for only a few months. A four-fold or greater increase in titer between acute and convalescent specimens confirms the diagnosis.

This test was developed and its performance characteristics have been determined by Quest Diagnostics Infectious Disease. It has not been cleared or approved by FDA. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

CHLAMYDOPHILA PNEUMONIAE ANTIBODIES (IgG, IgA, IgM)

REFERENCE RANGE: IgG <1:64
IgA <1:16
IgM <1:10

The immunofluorescent detection of specific antibodies to Chlamydophila pneumoniae may be complicated by cross-reactive antibodies, non-specific antibody stimulation, or past exposure to similar organisms such as C. psittaci and Chlamydia trachomatis. IgM titers of 1:10 or greater usually indicate recent infection, and any IgG titer may indicate past exposure. IgA is typically present at low titers during primary infection, but may be elevated in recurrent exposures or in chronic infection.

Myofibrillar Myopathy Panel (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

Myogenic Differentiation Antigen 1 (MYOD1) Immunostain, Technical Component Only

Clinical Information: Myogenic differentiation antigen 1 (MyoD1) is a myogenic nuclear regulatory protein that is normally expressed during embryogenesis. Nuclear expression of MyoD1 is restricted to myoblasts of developing skeletal muscle tissue. MyoD1 is present in the majority of rhabdomyosarcomas.

Useful For: Marker of skeletal muscle differentiation

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Myogenin Immunostain, Technical Component Only

**Clinical Information:** Myogenin is a member of a family of myogenic regulatory genes that include MyoD, myf5, and MRF4. These genes encode a set of transcription factors that are essential for muscle development. Expression of myogenin is restricted to cells showing skeletal muscle differentiation. Myogenin is found in the majority of rhabdomyosarcomas and Wilms tumors, and is absent in Ewing sarcoma and mature skeletal muscle.

**Useful For:** Marker of skeletal muscle differentiation

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

Myoglobin Immunostain, Technical Component Only

**Clinical Information:** Myoglobin is found in skeletal and cardiac muscle, but not in smooth muscle, and functions as an oxygen transporting pigment. Antibodies to myoglobin may be useful in the diagnosis of rhabdomyosarcomas, but the proportion of positive cells may be small, and they may be distributed unevenly in the section. Staining for myoglobin is not seen in carcinomas or in other sarcomas.

**Useful For:** Marker of skeletal and cardiac muscle

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

MYGLS

Myoglobin, Serum

Clinical Information: Myoglobin is a heme protein found in smooth and skeletal muscles. Serum myoglobin reflects a balance between intravascular release of myoglobin from muscle and renal clearance. Previously serum myoglobin had been advocated as a sensitive marker for early acute myocardial injury (eg, acute myocardial infarction: AMI). However, more recent studies indicate that other newer markers (eg, troponin) provide superior diagnostic utility in detecting early myocardial injury. Elevation of serum myoglobin may occur as a result of muscle trauma, resuscitation, myopathies, AMI, shock, strenuous body activity, or decreased elimination during renal insufficiency. Extreme elevations occur in rhabdomyolysis.

Useful For: Assessing muscle damage from any cause

Interpretation: Elevated myoglobin levels are seen in conditions of acute muscle injury.

Reference Values:
< or =90 mcg/L


MYGLU

Myoglobin, Urine

Clinical Information: Myoglobin is the oxygen-binding protein of striated muscle. Injury to skeletal or cardiac muscle results in the release of myoglobin. High concentrations appear very rapidly in the urine in various conditions including some metabolic diseases. Conditions associated with myoglobinuria include: -Hereditary myoglobinuria -Phosphorylase deficiency -Sporadic myoglobinuria -Exertional myoglobinuria in untrained individuals -Crush syndrome -Myocardial infarction -Myoglobinuria of progressive muscle disease -Heat injury Urine myoglobin increases with muscle necrosis, but the clinical consequences are variable. Therefore, myoglobin can confirm a clinical diagnosis of myopathy, but an elevated urine excretion of myoglobin is not specific for a clinical disorder. In acute renal failure, an elevated urinary myoglobin can suggest a potential cause and, consequently, may indicate appropriate treatment courses.

Useful For: Confirming the presence of a myopathy associated with any one of the disorders listed in Clinical Information May suggest a myopathic cause for acute renal failure

Interpretation: Increased excretion of urinary myoglobin suggests the disorders listed in Clinical Information. Most clinically significant elevations are elevated 2 to 10 times normal. Visual pigmenturia occurs at myoglobin concentrations about 160 times normal (approximately 4,000 mcg/L). Renal toxicity depends on multiple factors such as renal perfusion and degree of acidity of urine.

Reference Values:
< or =21 mcg/L

MyoMarker Panel 1

Reference Values:
Normal Range:  Negative

MyoMarker Panel 2

Clinical Information: 1. Anti-Jo 1 Abs are found in subset of myositis patients characterized by interstitial lung disease, systemic polyarthritis, Raynaud's Phenomena, fever and Mechanic's Hand (anti-synthetase syndrome). 2. Anti-Jo 1 appears to be a marker for interstitial lung disease in polymyositis. 3. The anti-PM/Scl-100 antibody is associated with younger age, calcinosis and has lower rates of gastrointestinal symptoms, ILD and pulmonary hypertension. There is also evidence of a possibly better survival compared to the presence of either anti-PM/Scl-75 or anti-Scl-70 antibodies.

Reference Values:
Mi-2, PL-12, PL-7, EJ, OJ, SRP, Ku, U2 snRNP

Reference Range: Negative

Anti-PM/Scl-100 Ab, Anti-Jo-1 Ab

Reference Range: <20

EIA Interpretation:

Negative: <20 units
Weak Positive: 20 - 39 units
Moderate Positive: 40 - 80 units
Strong Positive: >80 units

MyoMarker Panel 3

Clinical Information: 1. Anti-Jo 1 Abs are found in subset of myositis patients characterized by interstitial lung disease, systemic polyarthritis, Raynaud's Phenomena, fever and Mechanic's Hand (anti-synthetase syndrome). 2. Anti-Jo 1 appears to be a marker for interstitial lung disease in polymyositis. 3. The anti-PM/Scl-100 antibody is associated with younger age, calcinosis and has lower rates of gastrointestinal symptoms, ILD and pulmonary hypertension. There is also evidence of a possibly better survival compared to the presence of either anti-PM/Scl-75 or anti-Scl-70 antibodies.

Reference Values:
PL-7, PL-12, EJ, OJ, SRP, MI-2, Fibrillarin (U3 RNP), U2 snRNP, Ku:

Reference Range: Negative

Anti-Jo-1 Ab, TIF1 GAMMA (P155/140), MDA-5 (P140) (CADM-140), NXP-2 (P140), Anti-PM/Scl-100 Ab, Anti-U1-RNP Ab, Anti-SS-A 52 kD Ab IgG:

Reference Range: <20

EIA Interpretation:

Negative: <20 units
Weak Positive: 20 â€“ 39 units
Moderate Positive: 40 â€“ 80 units
### Myopathy Expanded Panel (Bill Only)

**Reference Values:**
- This test is for billing purposes only.
- This is not an orderable test.

### Myxoid/Round Cell Liposarcoma, 12q13 (DDIT3 or CHOP) Rearrangement, FISH, Tissue

**Clinical Information:** Myxoid/round cell liposarcoma is the second most common subtype of liposarcoma, accounting for more than one third of all liposarcomas and representing about 10% of all adult soft-tissue sarcomas. Myxoid/round cell liposarcoma is described as a malignant tumor composed of uniform round to oval shaped primitive nonlipogenic mesenchymal cells and a variable number of small signet-ring lipoblasts in a prominent myxoid stroma with a characteristic branching vascular pattern. A unique chromosome translocation, t(12;16)(q13;p11), resulting in a fusion of the DDIT3 gene (also known as CHOP or GADD153) on chromosome 12 and the FUS gene (also referred to as TLS) on chromosome 16, is the key genetic aberration in myxoid/round cell liposarcoma. More than 90% of myxoid/round cell liposarcoma are cytogenetically characterized by this translocation. In rare cases, a variant t(12;22)(q13;q12) has been described in which DDIT3 (CHOP) fuses with EWS, a gene highly related to FUS.

**Useful For:** Aiding in the diagnosis of myxoid/round cell liposarcoma by detecting a neoplastic clone associated with gene rearrangement involving the DDIT3 (CHOP) gene region at 12q13

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the DDIT3 (CHOP) probe. A positive result is consistent with a subset of myxoid/round cell liposarcoma. A negative result suggests no rearrangement of the DDIT3 (CHOP) gene region at 12q13. However, this result does not exclude the diagnosis of myxoid/round cell liposarcoma.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

### N-Acetylgalactosamine-6-Sulfatase, Leukocytes

**Clinical Information:** Mucopolysaccharidosis IVA, (MPS IVA, Morquio A syndrome) is an autosomal recessive mucopolysaccharidosis caused by reduced or absent N-acetylgalactosamine-6-sulfate sulfatase (GALNS) enzyme activity. The mucopolysaccharidoses are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAGs). Accumulation of GAGs (previously called mucopolysaccharides) in lysosomes interferes with normal functioning of cells, tissues, and organs. Clinical features and severity of symptoms of MPS IVA are widely variable and affect multiple body systems. Clinical features may include skeletal dysplasia, short stature, dental anomalies,
corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Treatment options are mostly limited to symptom management, however, more recently available enzyme replacement therapy has shown to be effective in improving some function and quality of life for individuals with Morquio A. Estimates of the incidence of Morquio A syndrome range from 1 in 200,000 to 1 in 300,000 live births. A diagnostic workup in an individual with MPS IVA typically demonstrates elevated levels of urinary GAGs and increased keratan sulfate and chondroitin-6-sulfate detected via quantitative and qualitative liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis of the specific sulfates. Morquio B is a genetically distinct disorder caused by a deficiency of beta-galactosidase and has a significant number of overlapping clinical features with Morquio A. Enzyme analysis is necessary to distinguish between the 2 types. Reduced or absent activity of N-acetylgalactosamine-6-sulfate sulfatase enzyme in leukocytes and/or fibroblasts can confirm a diagnosis of MPS IVA. Sequencing of the GALNS gene allows for detection of disease-causing mutations in affected patients and identification of familial mutations allows for testing of at-risk family members.

**Useful For:** Preferred test to rule-out mucopolysaccharidosis IVA (Morquio A syndrome) The test is not useful to establish carrier status for Morquio A syndrome.

**Interpretation:** Very low enzyme activity levels are consistent with Morquio A syndrome.

**Reference Values:**

> or =92 nmol/17 hour/mg protein

**Clinical References:**


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**N-Acetylgalactosamine-6-Sulfate Sulfatase, Fibroblasts**

**Clinical Information:** Mucopolysaccharidosis IVA, (MPS IVA, Morquio A syndrome) is an autosomal recessive mucopolysaccharidosis caused by reduced or absent N-acetylgalactosamine-6-sulfate sulfatase (GALNS) enzyme activity. The mucopolysaccharidoses are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans, GAGs). Accumulation of GAGs (previously called mucopolysaccharides) in lysosomes interferes with normal functioning of cells, tissues, and organs. Clinical features and severity of symptoms of MPS IVA are widely variable and affect multiple body systems. Clinical features may include skeletal dysplasia, short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Treatment options are mostly limited to symptom management, however, more recently available enzyme replacement therapy has shown to be effective in improving some function and quality of life for individuals with Morquio A. Estimates of the incidence of Morquio A syndrome range from 1 in 200,000 to 1 in 300,000 live births. A diagnostic workup in an individual with MPS IVA typically demonstrates elevated levels of urinary GAGs and increased keratan sulfate and chondroitin-6-sulfate detected via quantitative and qualitative liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis of the specific sulfates. Morquio B is a genetically distinct disorder caused by a deficiency of beta-galactosidase and has a significant number of overlapping clinical features with Morquio A. Enzyme analysis is necessary to distinguish between the 2 types. Reduced or absent activity of N-acetylgalactosamine-6-sulfate sulfatase enzyme in leukocytes or fibroblasts can confirm a diagnosis of MPS IVA. Sequencing of the GALNS gene allows for detection of disease-causing mutations in affected patients and identification of familial mutations allows for testing of at-risk family members.

**Useful For:** Assisting in the diagnosis of Morquio A syndrome in fibroblast specimens The test is not useful to establish carrier status for Morquio A syndrome.

**Interpretation:** Very low enzyme levels are consistent with Morquio A disease.
**Reference Values:**

> or =163 nmol/17 hour/mg protein

**Clinical References:**

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**NAPRO**

N-acetylprocainamide, Serum

**Reference Values:**

Only orderable as part of a profile. For more information see PROCG / Procainamide and NAPA, Serum.

---

**NAT2**

N-Acetyltransferase 2 Gene (NAT2), Full Gene Sequence

**Clinical Information:** Aryamine N-acetyltransferase type 2 (NAT2) is a highly polymorphic phase 2 metabolic enzyme that conjugates hydrazine derivatives and aromatic amine drugs with acetyl-groups. NAT2 also is involved in the acetylation and activation of some procarcinogens. (1) Individuals acetylate drugs at different rates by NAT2, and are described as having slow, intermediate, or fast acetylator phenotypes. A gradient exists in which the prevalence of slow acetylator phenotypes increases with decreasing distance to the equator. Near the equator, up to 80% of individuals may be slow acetylators, while in some more northern countries, as few as 10% of the population may have the slow acetylator phenotype. A number of drugs are metabolized by NAT2 including procainamide, dapsone, nitrazepam, hydralazine, zonisamide, and isoniazid. Isoniazid is used to treat and prevent tuberculosis, and is still used as a primary treatment agent. Adverse reactions with isoniazid, which include nausea, drug-induced hepatitis, peripheral neuropathy, and sideroblastic anemia, are associated more often with a slow NAT2 acetylator phenotype. These individuals may require a lower dose to avoid adverse reactions. The NAT2 gene contains a single intronless exon of 870 base pairs and encodes 290 amino acids. NAT2 is highly polymorphic and contains 16 known single nucleotide polymorphisms (SNPs) and 1 single base pair deletion. These polymorphisms are combined into 36 known haplotype alleles. Each individual haplotype is predictive of either a fast or slow acetylator phenotype. Individuals with 2 fast haplotypes are predicted to be extensive (normal) metabolizers, while those with 1 fast and 1 slow haplotype are intermediate metabolizers, and those with 2 slow haplotypes are poor metabolizers. (2,3) Studies with patients who have different acetylator haplotypes have correlated the ratio of plasma N-acetylsisoniazid/isoniazid drug concentrations with haplotypes, with slow and intermediate acetylators having lower ratios than fast acetylators. (4) NAT2 Allele Nucleotide Change Amino Acid Change Predicted Acetylator Phenotype 

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<tr>
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<th>Amino Acid Change</th>
<th>Predicted Acetylator Phenotype</th>
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**Useful For:** Identifying patients who may require isoniazid dosing adjustments
Interpretation: The wild-type (normal) genotype for NAT2 is *4. This is the most commonly occurring allele in some, but not all, ethnic groups. Individuals are classified as being slow, intermediate, or fast acetylators depending on their diplotypes. Slow acetylators have 2 slow haplotypes, fast acetylators have 2 fast haplotypes, and intermediate acetylators have 1 of each. Slow acetylators receiving isoniazid therapy should be monitored for signs of toxicity. Dose reductions may be considered for both slow and intermediate acetylators. However, it should be verified that the reduced isoniazid dose produces serum levels within the therapeutic range.

Reference Values:
An interpretive report will be provided.

Clinical References:

NAT2O
60345

N-Acetyltransferase 2 Gene (NAT2), Full Gene Sequence, Saliva


**Useful For:** Identifying patients who may require isoniazid dosing adjustments Genotyping patients who prefer not to have venipuncture done

**Interpretation:** The wild-type (normal) genotype for NAT2 is *4. This is the most commonly occurring allele in some, but not all, ethnic groups.(5) Individuals are classified as being slow, intermediate, or fast acetylators depending on their diplotype. Slow acetylators have 2 slow haplotypes, fast acetylators have 2 fast haplotypes, and intermediate acetylators have 1 of each. Slow acetylators receiving isoniazid therapy should be monitored for signs of toxicity. Dose reductions may be considered for both slow and intermediate acetylators. However, it should be verified that the reduced isoniazid dose produces serum levels within the therapeutic range.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**N-Methylhistamine, 24 Hour, Urine**

**Clinical Information:** N-methylhistamine (NMH) is the major metabolite of histamine, which is produced by mast cells. Increased histamine production is seen in conditions associated with increased mast-cell activity, such as allergic reactions, but also in mast-cell proliferation disorders, in particular mastocytosis. Mastocytosis is a rare disease. Its most common form, urticaria pigmentosa (UP), affects the skin and is characterized by multiple persistent small reddish-brown lesions that result from infiltration of the skin by mast cells. Systemic mastocytosis is caused by the accumulation of mast cells in other tissues and can affect organs such as the liver, spleen, bone marrow, and small intestine. The mast-cell proliferation in systemic mastocytosis can be either benign or malignant. In children, benign systemic mastocytosis tends to resolve over time, while in most, but not all adults, the disease is progressive. Systemic mastocytosis may or may not be accompanied by UP.(1,3) Patients with UP or systemic mastocytosis can have symptoms ranging from itching, gastrointestinal distress, bone pain, and headaches; to flushing and anaphylactic shock. Diagnosis of mastocytosis is made by bone marrow biopsy; however, patients with systemic mastocytosis usually exhibit elevated levels of NMH.(1-5) Other biochemical markers include 11-beta prostaglandin F(2) alpha, a metabolite of prostaglandin D2 (23BPG / 2,3 Dinor-11Beta-Prostaglandin F2 Alpha, Urine), and tryptase, alpha or beta (TRYPT / Tryptase, Serum).

**Useful For:** Screening for and monitoring of mastocytosis and disorders of systemic mast-cell activation, such as anaphylaxis and other forms of severe systemic allergic reactions Monitoring therapeutic progress in conditions that are associated with secondary, localized, low-grade persistent, mast-cell proliferation and activation such as interstitial cystitis

**Interpretation:** Increased concentrations of urinary N-methylhistamine (NMH) are consistent with urticaria pigmentosa (UP), systemic mastocytosis, or mast-cell activation. Because of its longer half-life, urinary NMH measurements have superior sensitivity and specificity than histamine, the parent compound. However, not all patients with systemic mastocytosis or anaphylaxis will exhibit...
concentrations outside the reference range and healthy individuals may occasionally exhibit values just above the upper limit of normal. The extent of the observed increase in urinary NMH excretion is correlated with the magnitude of mast-cell proliferation and activation; UP patients, or patients with other localized mast-cell proliferation and activation, show usually only mild elevations, while systemic mastocytosis and anaphylaxis tend to be associated with more significant rises in NMH excretion (2-fold or more). There is, however, significant overlap in values between UP and systemic mastocytosis, and urinary NMH measurements should not be relied upon alone in distinguishing localized from systemic disease. Up to 25% variability in spot-urine excreted levels may be observed, making 24-hour urine collections preferable for cases with borderline results. Children have higher NMH levels than adults. By the age of 16, adult levels have been reached.

**Reference Values:**
- 0-5 years: 120-510 mcg/g creatinine
- 6-16 years: 70-330 mcg/g creatinine
- >16 years: 30-200 mcg/g creatinine

**Clinical References:**

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**N-terminal Telopeptide (NTx), Serum**

**Clinical Information:** Human bone is continuously remodeled through the process of bone formation and resorption. Measurement of bone turnover markers (BTM) in serum or urine serves as an indicator of bone formation or bone resorption cellular activities. BTM are physiologically elevated during childhood, growth, and during fracture healing. The elevations in bone resorption markers and bone formation markers are typically balanced in these circumstances and of no diagnostic value. Bone diseases occur when formation and resorption are uncoupled. In these situations, BTM might serve as predictors of therapy response. Telopeptides of type 1 collagen are the most extensively studied and used bone resorption markers. There are 2 forms depending on the cross-link forming site with collagen: the N-terminal telopeptide (NTx) and C-terminal telopeptide (CTX), which are released during collagen degradation. In osteoporosis, a disease characterized by low bone mass and deterioration of bone tissue leading to increase skeletal fragility, measurement of BTM helps to determine treatment efficacy or patientâ€™s compliance with therapy. The advantage of measurement of BTM is that changes in response to therapy are observed within 3 to 6 months after therapy initiation; whereas changes in bone mineral density are not observed until 12 to 24 months posttherapy. Other diseases affecting the bone remodeling process, such as hyperthyroidism, all forms of hyperparathyroidism, most forms of osteomalacia and rickets (even if not associated with hyperparathyroidism), hypercalcemia of malignancy, Paget disease, multiple myeloma, bony metastases, as well as various congenital diseases of bone formation and remodeling, can result in accelerated and unbalanced bone turnover and elevation of BTM.

**Useful For:** Monitoring effectiveness of antiresorptive therapy in patients treated for osteoporosis or other metabolic bone disorders As an adjunct in the diagnosis of medical conditions associated with increased bone turnover

**Interpretation:** Elevated levels of N-terminal telopeptide (NTx) indicate increased bone resorption. A 30% or greater reduction in this resorption marker 3 to 6 months after initiation of therapy indicates a probably adequate therapeutic response. A common target of antiresorptive therapy in the treatment of postmenopausal osteoporosis is to achieve bone markers concentrations within the premenopausal...
Reference range.

**Reference Values:**
All units are reported in nmol Bone Collagen Equivalents (BCE)
 Adult (> or =18 years of age)

Males:
5.4-24.2 nmol BCE

Females:
Premenopausal: 6.2-19.0 nmol BCE
The target value for postmenopausal adult females undergoing treatment for osteoporosis is the same as the premenopausal reference interval.

**Clinical References:**

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**FINA 91447**

**NAbFeron (IFNB-1) Neutralizing Antibody Test**

**Useful For:** Detection of antibodies to interferon-B-1

**Reference Values:**
Final report has been sent to the referring laboratory.

**Clinical References:**

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**FNAD 80761**

**Nadolol, Serum/Plasma**

**Reference Values:**
Reporting limit determined each analysis

**Synonym(s):** Corgard

Mean steady-state plasma levels following a daily regimen:
- 80 mg: 26 â€“ 36 ng/mL
- 160 mg: 52 â€“ 74 ng/mL
- 320 mg: 154 â€“ 191 ng/mL

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**FNALO 91784**

**Naloxone - Total (Conjugated/Unconjugated), Screen, Urine**

**Reference Values:**
Reporting limit determined each analysis (screen and confirmation)

**Naloxone â€“ Total ng/mL**

**Synonym(s):** Narcan

**Naloxone â€“ Confirmation ng/mL**

**Synonym(s):** Narcan
**NAPSN 70519**

**Napsin A Immunostain, Technical Component Only**

**Clinical Information:** Napsin A is an aspartic proteinase involved in the proteolytic processing of surfactant precursors in the normal alveolar epithelium. In normal tissues, napsin A is expressed in the cytoplasm of alveolar macrophages, type II pneumocytes, pancreatic ducts and acini, and in renal tubules. Napsin A has clinical utility for the identification of primary lung adenocarcinomas. Napsin A is also positive in a subset of thyroid and renal cell carcinomas (especially papillary types).

**Useful For:** Aids in the identification of primary lung adenocarcinoma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**NARC 82026**

**Narcolepsy-Associated Antigen, HLA-DQB1 Typing, Blood**

**Clinical Information:** Narcolepsy is a neurological condition affecting about 0.02% of African American, Caucasian, and Japanese individuals. It is characterized by excessive daytime somnolence and abnormal rapid eye movement (REM) sleep. Cataplexy (weakness precipitated by emotions, especially laughter) is present in 64% to 79% of patients with narcolepsy. Studies have identified DQB1*06:02 as a useful marker of narcolepsy. DQB1*06:02 is found in 90% to 95% of African American, Caucasian, and Japanese patients with narcolepsy who also have cataplexy (narcolepsy type 1), but only in 45% to 50% of patients with narcolepsy without cataplexy (narcolepsy type 2). It must also be clearly understood that about 25% of normal people have this gene. Because DQB1*06:02 is present in the normal population, no test for an HLA gene constitutes a test for narcolepsy. A more reliable approach would be to consider that, in an appropriate patient who has cataplexy, the absence of the strongly associated DQB1*06:02, provides good evidence that the patient does not have narcolepsy. However, its absence does not rule-out narcolepsy without cataplexy (narcolepsy type 2).

**Useful For:** Ruling out a diagnosis of narcolepsy

**Interpretation:** If DQB1*06:02 is not detected, the narcolepsy-associated antigen test result will be reported as negative for DQB1*06:02. If the allele is detected, the result will be reported as positive for DQB1*06:02.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**
**NASH FibroSure**

**Useful For:** This test is a noninvasive assessment of liver status in patients with nonalcoholic fatty liver disease (NAFLD). Quantitative results of 10 biochemicals in combination with age, gender, height and weight are analyzed using a computational algorithm to provide a quantitative surrogate marker (0.0-1.0) of liver fibrosis (Metavir F0-F4), hepatic steatosis (0.0-1.0, S0-S3), and nonalcoholic steatohepatitis (NASH) (0.0-0.75, N0-N2). The absence of steatosis (S<0.38) precludes the diagnosis of NASH.

**Interpretation:** Quantitative results of 10 biochemical in combination with age, gender, height, and weight, are analyzed using a computational algorithm to provide a quantitative surrogate marker (0.0-1.0) of liver fibrosis (Metavir F0-F4), hepatic steatosis (0.0-1.0, S0-S3), and Non-Alcoholic Steato-Hepatitis (NASH) (0.0-0.75, N0-N2). The absence of steatosis (S<0.38) precludes the diagnosis of NASH. Fibrosis marker: In a study of 171 Non-Alcoholic Fatty Liver Disease (NAFLD) patients where 23% had significant NAFLD fibrosis (Metavir F2-F4) and 11% had cirrhosis by liver biopsy, a fibrosis result of >0.3 yielded a sensitivity of 83% and a specificity of 78% for the detection of significant fibrosis (1). Steatosis Marker: In a population of 744 patients (583 HCV, 18 HBV, 69 NAFLD, and 74 alcoholic disease patients), where 36% had significant steatosis (>5%) on a liver biopsy, a steatosis score >0.5 had a sensitivity of 71% and a specificity of 72% for identification of significant steatosis (2). NASH marker: In a population of 257 NAFLD patients, where 62% had at least some NASH by liver biopsy, a prediction of NASH had a sensitivity of 88% for identifying NASH and a specificity of 50% (3). Fibrosis Scoring: <0.21 = Stage F0 - No fibrosis 0.21 - 0.27 = Stage F0 - F1 0.27 - 0.31 = Stage F1 - Portal fibrosis 0.31 - 0.48 = Stage F1 - F2 0.48 - 0.58 = Stage F2 - Bridging fibrosis with few septa 0.58 - 0.72 = Stage F3 - Bridging fibrosis with many septa 0.72 - 0.74 = Stage F3 - F4 >0.74 = Stage F4 â€“ Cirrhosis Steatosis Grading <0.30 = S0 - No Steatosis 0.30 to 0.38 = S0 â€“ S1 0.38 to 0.48 = S1 - Minimal Steatosis 0.48 to 0.57 = S1 â€“ S2 0.57 to 0.67 = S2 â€“ S3 >0.69 = S3 â€“ Marked or Severe Steatosis NASH Scoring 0.25 = N0 - Not NASH 0.50 = N1 - Borderline or probable NASH 0.75 = N 2 - NASH

**Reference Values:**

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<td>Steatosis Score</td>
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<td>Glucose, Serum</td>
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Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  Page 1620
Triglycerides 0-149 mg/dL

Limitations: NASH FibroSure is recommended for patients with suspected nonalcoholic fatty liver disease. It is not recommended for patient with other liver diseases. It is also not recommended in patients with Gilbert disease, acute hemolysis, acute viral hepatitis, drug induced hepatitis, genetic liver disease, autoimmune hepatitis and/or, extra-hepatic cholestasis. Any of these clinical situations may lead to inaccurate quantitative predictions of fibrosis.


Natural Killer (NK)/Natural Killer T (NKT) Cell Subset Panel

Clinical Information: Natural killer (NK) cells are derived from pluripotent hematopoietic stem cell precursors, but develop independently of the thymus. They comprise a key lymphocyte subset (approximately 10%-15% of peripheral blood mononuclear cells) and are a constituent of the innate immune system, since these cells do not rearrange their germline DNA to obtain specificity. NK cells serve an important role in host defense against viral infections, as well as tumor surveillance. They are also a component of the adaptive immune response through cytokine production. NK cell functions are governed by a balance between activating receptors and inhibitory receptors. NK cells are identified by expression of different cell-surface receptors and they are not a homogeneous population.(1) In general, the most common combination of surface markers used to identify the majority of NK cells is the absence of CD3 (CD3-), along with expression of CD56 (neural cell adhesion molecule) and CD16 (low-affinity IgG Fc receptor-FcgammaRIII). However, not all NK cells express the CD56 and CD16 markers uniformly and, therefore, can be divided into subsets based on expression of these 2 molecules.(2) The CD16+ CD56+/− (dim or negative) that are CD3- are referred to as cytotoxic NK cells, while the CD56+ (bright) CD16- NK cells are called regulatory or cytokine secreting NK cells.(3) These are not only phenotypically and functionally distinct subsets but also developmentally separate. The majority of human NK cells (approximately 90%) have dim expression of CD56 and moderate to high levels of CD16, as well as perforin and granzymes (2 proteins mediating cytolytic activity), and are therefore high in cytotoxic capability. The remaining minority (approximately 10%) of NK cells are the CD56(bright) cytokine-producing NK cells. Therefore, cytotoxicity and cytokine production are the major functions of NK cells. Cytotoxicity can be subdivided into (1) natural cytotoxicity directed largely toward virally infected cells or tumor cells, in the absence of prior stimulation or immunization, and (2) antibody-dependent cellular cytotoxicity (ADCC) directed against antibody-coated target cells.(4) Circulating NK cells are enriched for the CD56(dim) phenotype, while within the lymph nodes, NK cells are largely CD56(bright). This differential localization is related to the pattern of homing receptors expressed on NK cells: CD56(dim) NK cells express homing markers for inflamed peripheral sites, while CD56(bright) NK cells express receptors for secondary lymphoid organs. The majority of circulating human NK cells, which have cytotoxic function and phenotype (CD56(dim)), are CD27-, while the CD56(bright) cells are CD27+. Therefore, the absence of CD27 expression identifies cytotoxic effector cells within the mature NK cell subsets.(5) Other markers are: -NKp46 (CD335) is a marker expressed on the majority of human NK cells and is an activating receptor involved in non-major histocompatibility complex (MHC)-restricted natural NK cytotoxicity. It is expressed in all resting and activated NK cells, including the minor CD56(bright) cytokine-producing population.
NKp46 is considered to be involved in tumor cell eradication in vivo. -NKG2D is an activating receptor expressed on all NK cells, as well as on natural killer T (NKT) cells. NKG2D has been described as being relevant in tumor surveillance and organ transplantation.(6) -CD69 is a marker for NK-cell activation and triggers NK-mediated cytolytic activity and sustains NK-cell activation.(7) -CD95 (Fas or APO-1) is a marker expressed on a variety of immune cells, including lymphocytes and NK cells. CD95 is involved in mediating programmed cell death or apoptosis and has been shown to associate with NK cell regulatory function in multiple sclerosis.(8) -CD107a and CD107b (lysosomal-associated membrane proteins 1 and 2: LAMP-1 and LAMP-2) expression are markers of NK cell functional activity and correlate with both cytokine production and NK-cell-mediated lysis of target cells.(9) -Perforin, granzyme A, and granzyme B are components of the cytolytic granules in NK cells and associated with NK cell cytotoxic function, while interferon gamma (IFN-gamma) is produced by NK cells on activation.(10) -NK cells also secrete other cytokines including tumor necrosis factor alpha (TNF-alpha), interleukin-1 (IL-1), IL-3, and granulocyte monocyte-colony stimulating factor (GM-CSF). NKT cells represent a specialized T-cell population that is distinct from conventional T cells. They express an invariant T-cell receptor (TCR) that recognizes self and bacterial glycosphingolipid antigens presented by the MHC class I-like molecule, CD1d.(11) The development of NKT cells is also unique from regular T cells, as NKT cell precursors are positively selected by CD4+CD8+ cortical thymocytes and the signaling pathways differ from the conventional T cells. Activated NKT cells rapidly produce large amounts of Th1 and Th2 cytokines that transactivate other immune components and, therefore, NK cells are involved in both innate and adaptive immune responses.(11) NK cell deficiencies can be present as part of a larger immunological syndrome or as an isolated deficiency. Some of the primary (monogenic) immunodeficiencies that affect NK cell function or numbers include autoimmune lymphoproliferative syndrome (ALPS) related to CASP8 (caspase 8 mutations); familial hemophagocytic lymphohistiocytosis (FHL) types 2, 3, and 4 due to mutations in the PFP1 (encoding perforin), UNC13D (encoding the Munc13-4 protein), and STX-11 (encoding syntaxin -11), respectively; Hermansky-Pudlak syndrome (AP3B1); Papillon-Lefèvre syndrome (CTSC, cathepsin C); nuclear factor kappa-beta essential modulator deficiency (NEMO) due to mutations in the IKBKG gene; severe combined immunodeficiencies due to mutations in the IL-2RG, JAK3, ADA, PNP, ADK2 genes; bare lymphocyte syndrome (TAP2 gene); X-linked inhibitor of apoptosis deficiency (XIAP gene); X-linked lymphoproliferative disease (XLP): XLP-1 (due to mutations in the SAP gene); Griscelli syndrome (RAB27A gene); Chediak-Higashi syndrome (LYST gene); and Wiskott-Aldrich syndrome (WAS gene).(12) Patients with X-linked inhibitor of apoptosis protein (XIAP) deficiency have been variably reported as having either normal numbers of NKT cells (13) or low numbers of NKT cells.(14) The apparent discrepancy in the numbers of NKT cells is likely related to the difference in size of the sample control groups and disease stage of patients between the 2 reports. At the present time, the role of XIAP in development of NKT cells has not been clearly delineated. The isolated NK cell deficiencies include the absolute NK cell deficiency (ANKD), the classic NK cell deficiency (CNKD), and the functional NK cell deficiency (FNKD). NK cell function is absent in ANKD and CNKD and deficient in FNKD, while NK cells are present in the latter, but absent in the former 2 conditions. NKT cells are absent only in ANKD and present in both CNKD and FNKD.(12) NK cell dysfunction has also been reported in systemic juvenile rheumatoid arthritis and macrophage activation syndrome.(15) There is also more data emerging on the pathogenic role of NK cells in atopic and autoimmune diseases.(4) HIV-1 patients show a gradual loss of NK cells that correlates with disease progression. There is a selective loss of CD56(dim) NK cells, while the numbers of CD56(bright) NK cells remain the same. There appears to be a defect in differentiation from immature CD56- NK cells to mature CD56(dim) NK cells (16), with an expansion of the former (CD56-CD16+) NK cells in HIV viremic patients.(17) Differential mobilization of NK-cell subsets has also been reported related to acute exercise, with CD56(bright) NK cells being less responsive than CD56(dim) NK cells and the ratio of CD56(bright):CD56(dim) favors the former at least up to 1-hour postexercise.(18) NK cells also play an important role in regulating viral infections, and their deficiency predisposes to susceptibility with herpes virus infections. NKG2D expression has been reported to decrease during human CMV infection.(19) NK cells that express inhibitory receptors to self-MHC class I molecules are called "licensed," which means they are functionally more responsive to stimulation, while "unlicensed" NK cells lack receptors for self-MHC class I and are hyporesponsive. Contrary to the hypothesis that "licensed" NK cells are key for viral immunity, the depletion of "unlicensed" NK cells impairs control of viremia, suggesting that these cells are critical for protection against viral infection. NK-cell lymphocytosis is seen in NK-neoplasias, extranodal NK/T-cell lymphoma, aggressive NK-cell leukemia, and blastic NK-cell lymphoma. Chronic NK-cell lymphocytosis (CNKL) is an indolent
disorder characterized by proliferation of CD3-CD56+CD16- NK cells. Epstein-Barr virus (EBV) can infect nonneoplastic NK cells(20), and there is an expansion of CD16+CD56(dim) NK cells. Chronic active EBV infection involving NK cells can present with severe inflammatory and necrotic skin reactions typically associated with EBV+ NK-cell lymphoproliferative disease.(21) This assay provides both absolute and relative quantitation of various NK-cell subsets relative to total NK cells (NK cell subsets) or total lymphocytes (NKT cells) and can be used for assessment in the following clinical contexts: HIV, primary immune deficiencies with NK cell defects, NK-cell lymphocytosis, solid-organ transplantation, immune reconstitution following bone marrow or hematopoietic cell transplantation, evaluation of NK cells in neoplasias, only for quantitation (not for diagnosis or classification of NK cell malignancies).

**Useful For:** Quantitation of natural killer (NK)/natural killer T (NKT) cell subsets as well as quantitation of specific cell-surface and intracellular proteins required for NK cell function

**Interpretation:** Interpretive comments will be provided, where applicable, along with reference range values for adult samples. Since a separate pediatric reference range could not be established at this time, interpretation of pediatric samples will be made using the adult reference range as an approximate guideline. For the surface marker and intracellular protein expression on natural killer (NK) subsets, relevant values that are abnormal will be provided in a table format within the interpretation along with textual interpretive comments. If results for surface and/or intracellular subsets are quantitatively normal, then only interpretive comments will be provided without actual numeric data. Clients may request numerical data for specific subsets that are not included within the report through the Laboratory Director.

**Reference Values:**
The appropriate age-related reference values will be provided on the report. Pediatric reference values are not available and therefore, interpretation will be based on adult ranges with appropriate cautionary statements in the interpretation.

**Clinical References:**

Natural Killer (NK)/Natural Killer T (NKT) Cell Subsets, Quantitative

Clinical Information: Natural killer (NK) cells are derived from pluripotent hematopoietic stem cell precursors, but develop independently of the thymus. They comprise a key lymphocyte subset (approximately 10%-15% of peripheral blood mononuclear cells) and are a constituent of the innate immune system, since these cells do not rearrange their germline DNA to obtain specificity. NK cells serve an important role in host defense against viral infections, as well as tumor surveillance. They are also a component of the adaptive immune response through cytokine production. NK cell functions are governed by a balance between activating receptors and inhibitory receptors. NK cells are identified by expression of different cell-surface receptors and they are not a homogeneous population.(1) In general, the most common combination of surface markers used to identify the majority of NK cells is the absence of CD3 (CD3-), along with expression of CD56 (neural cell adhesion molecule) and CD16 (low-affinity IgG Fc receptor-Fe gamma RIII). However, not all NK cells express the CD56 and CD16 markers uniformly and, therefore, can be divided into subsets based on expression of these 2 molecules.(2) The CD16+ CD56+-/- (dim or negative) that are CD3- are referred to as cytotoxic NK cells, while the CD56+ (bright) CD16- NK cells are called regulatory or cytokine secreting NK cells.(3) These are not only phenotypically and functionally distinct subsets but also developmentally separate. The majority of human NK cells (approximately 90%) have dim expression of CD56 and moderate to high levels of CD16, as well as perforin and granzymes (2 proteins mediating cytolitic activity), and are therefore high in cytotoxic capability. The remaining minority (approximately 10%) of NK cells are the CD56(bright) cytokine-producing NK cells. Therefore, cytotoxicity and cytokine production are the major functions of NK cells. Cytotoxicity can be subdivided into (1) natural cytotoxicity directed largely toward virally infected cells or tumor cells, in the absence of prior stimulation or immunization, and (2) antibody-dependent cellular cytotoxicity (ADCC) directed against antibody-coated target cells.(4) Circulating NK cells are enriched for the CD56(dim) phenotype, while within the lymph nodes, NK cells are largely CD56(bright). This differential localization is related to the pattern of homing receptors expressed on NK cells: CD56(dim) NK cells express homing markers for inflamed peripheral sites, while CD56(bright) NK cells express receptors for secondary lymphoid organs. The majority of circulating human NK cells, which have cytotoxic function and phenotype (CD56(dim)), are CD27-, while the CD56(bright) cells are CD27+. Therefore, the absence of CD27 expression identifies cytotoxic effector cells within the mature NK cell subsets.(5) Natural killer T (NKT) cells represent a specialized T-cell population that is distinct from conventional T cells. Some of the primary (monogenic) immunodeficiencies that affect NK cell function or numbers include autoimmune lymphoproliferative syndrome (ALPS) related to CASP8 (caspase 8 mutations); familial hemophagocytic lymphohistiocytosis (FHL) types 2, 3, and 4 due to mutations in the PFP1 (encoding perforin), UNCG13D (encoding the Munc13-4 protein) and STX-11 (encoding syntaxin -11), respectively; Hermansky-Pudlak syndrome (AP3B1); Papillon-Lefevre syndrome (CTSC, cathepsin C); nuclear factor kappa-beta essential modulator deficiency (NEMO) due to mutations in the IKBKG gene; severe combined immunodeficiencies due to mutations in the IL-2RG, JAK3, ADA, PNP, ADK2 genes; bare lymphocyte syndrome (TAP2 gene); X-linked inhibitor of apoptosis deficiency (XIAP gene); X-linked lymphoproliferative disease (XLP): XLP-1 (due to mutations in the SAP gene); Griscelli syndrome (RAB27A gene); Chediak-Higashi syndrome (LYST gene); and
Wiskott-Aldrich syndrome (WAS gene).(12) Patients with X-linked inhibitor of apoptosis protein (XIAP) deficiency have been variably reported as having either normal numbers of NKT cells (13) or low numbers of NKT cells.(14) The apparent discrepancy in the numbers of NKT cells is likely related to the difference in size of the sample control groups and disease stage of patients between the 2 reports. At the present time, the role of XIAP in development of NKT cells has not been clearly delineated. The isolated NK cell deficiencies include the absolute NK cell deficiency (ANKD), the classic NK cell deficiency (CNKD), and the functional NK cell deficiency (FNKD). NK cell function is absent in ANKD and CNKD and deficient in FNKD, while NK cells are present in the latter but absent in the former 2 conditions. NKT cells are absent only in ANKD and present in both CNKD and FNKD.(12) NK cell dysfunction has also been reported in systemic juvenile rheumatoid arthritis and macrophage activation syndrome.(15) There is also more data emerging on the pathogenic role of NK cells in atopic and autoimmune diseases.(4) HIV-1 patients show a gradual loss of NK cells that correlates with disease progression. There is a selective loss of CD56(dim) NK cells, while the numbers of CD56(bright) NK cells remain the same. There appears to be a defect in differentiation from immature CD56- NK cells to mature CD56(dim) NK cells (16), with an expansion of the former (CD56-CD16+) NK cells in HIV viremic patients.(17) Differential mobilization of NK-cell subsets has also been reported related to acute exercise, with CD56(bright) NK cells being less responsive than CD56(dim) NK cells and the ratio of CD56(bright):CD56(dim) favors the former at least up to 1-hour post-exercise.(18) NK cells also play an important role in regulating viral infections, and their deficiency predisposes to susceptibility with herpes virus infections. NKG2D expression has been reported to decrease during human CMV infection.(19) NK cells that express inhibitory receptors to self-MHC class I molecules are called "licensed," which means they are functionally more responsive to stimulation, while "unlicensed" NK cells lack receptors for self-MHC class I and are hyporesponsive. Contrary to the hypothesis that "licensed" NK cells are key for viral immunity, the depletion of "unlicensed" NK cells impairs control of viremia, suggesting that these cells are critical for protection against viral infection. NK cell lymphocytosis is seen in NK-neoplasias, extranodal NK/T-cell lymphoma, aggressive NK-cell leukemia, and blastic NK-cell lymphoma. Chronic NK-cell lymphocytosis (CNKL) is an indolent disorder characterized by proliferation of CD3-CD56+CD16- NK cells. Epstein-Barr virus (EBV) can infect nonneoplastic NK cells(20), and there is an expansion of CD16+CD56(dim) NK cells. Chronic active EBV infection involving NK cells can present with severe inflammatory and necrotic skin reactions typically associated with EBV+ NK-cell lymphoproliferative disease.(21)

**Useful For:** Quantitation of ONLY the major natural killer (NK)-cell subsets relative to total NK cells (NK cell subsets) or total lymphocytes (NK T cells) Assessment in the following clinical contexts: HIV, primary immune deficiencies with NK cell defects, NK-cell lymphocytosis, solid-organ transplantation, immune reconstitution following bone marrow or hematopoietic cell transplantation, evaluation of NK cells in neoplasias

**Interpretation:** Interpretive comments will be provided, where applicable, along with reference range values for adult samples. Since a separate pediatric reference range could not be established at this time, interpretation of pediatric samples will be made using the adult reference range as an approximate guideline.

**Reference Values:**
The appropriate age-related reference values will be provided on the report. Pediatric reference values are not available and therefore, interpretation will be based on adult ranges with appropriate cautionary statements in the interpretation.

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| NEGCT   | 70410 | Negative Control, Technical Component Only | |

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Clinical Information: Patterns of protein expression as determined by immunohistochemistry can be useful for pathologic diagnosis and classification.

Useful For: Qualitative detection of protein expression within cells in paraffin-embedded tissues

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

GCRNA 61552

Neisseria gonorrhoeae by Nucleic Acid Amplification (HOLOGIC)

Clinical Information: Gonorrhea is caused by the bacterium Neisseria gonorrhoeae, which is a common sexually transmitted infection (STI).(1,2) Many infections in women are asymptomatic and the true prevalence of gonorrhea is likely much higher than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria and vaginal, urethral, and/or rectal discharge. Potential complications include pelvic inflammatory disease in women and gonococcal epididymitis and prostatitis in men. Gonococcal bacteremia, pharyngitis, and arthritis may also occur. Infection in men is typically associated with symptoms that would prompt clinical evaluation. Given the risk for asymptomatic infection in women, screening is recommended for women at increased risk of infection (e.g., women with previous gonorrhea or other STI, inconsistent condom use, new or multiple sex partners, and women in certain demographic groups, such as those in communities with high STI prevalence).(1,2) Routine bacterial culture was previously considered the gold standard test for diagnosis of Neisseria gonorrhoeae infection. However, organisms are labile in vitro, therefore, precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now the recommended method for diagnosis in most cases.(2-5) Immunoassays and nonamplification DNA tests are also available for Neisseria gonorrhoeae detection, but these methods are significantly less sensitive and specific than NAAT.(2-5) Improved screening and performance of NAAT testing has resulted in an increased number of accurately diagnosed cases.(2-5) Improved detection rates result from both the increased performance of the assay and the patients’ easy acceptance of urine testing. Early identification of infection enables sexual partners to seek testing and treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of complications in women.

Useful For: Detection of Neisseria gonorrhoeae

Interpretation: A positive result indicates the presence of rRNA of Neisseria gonorrhoeae. A negative result indicates that rRNA for Neisseria gonorrhoeae was not detected in the specimen. The predictive value of an assay depends on the prevalence of the disease in any particular population. In settings with a high prevalence of sexually transmitted disease, positive assay results have a high likelihood of being true-positives. In settings with a low prevalence of sexually transmitted disease, or in any settings in which a patient’s clinical signs and symptoms or risk factors are inconsistent with gonococcal or chlamydial urogenital infection, positive results should be carefully assessed and the patient retested by other methods (eg, culture for Neisseria gonorrhoeae), if appropriate.

Reference Values:
Negative

Neisseria gonorrhoeae, Miscellaneous Sites, by Nucleic Acid Amplification

Clinical Information: Gonorrhea is caused by the bacterium Neisseria gonorrhoeae. It is also a very common sexually transmitted infection (STI), with 301,174 cases of gonorrhea reported to CDC in 2009.(1,2) Many infections in women are asymptomatic and the true prevalence of gonorrhea is likely much higher than reported. The organism causes genitourinary infections in women and men and may be associated with dysuria and vaginal, urethral, or rectal discharge. Complications include pelvic inflammatory disease in women and gonococcal epididymitis and prostatitis in men. Gonococcal bacteremia, pharyngitis, and arthritis may also occur. Infection in men is typically associated with symptoms that would prompt clinical evaluation. Given the risk for asymptomatic infection in women, screening is recommended for women at increased risk of infection (eg, women with previous gonorrhea or other STI, inconsistent condom use, new or multiple sex partners, and women in certain demographic groups such as those in communities with high STI prevalence).(1,2) The CDC currently recommends dual antibiotic treatment due to emerging antimicrobial resistance.(2) Culture was previously considered to be the gold standard test for diagnosis of N gonorrhoeae infection. However, organisms are labile in vitro, and precise specimen collection, transportation, and processing conditions are required to maintain organism viability, which is necessary for successful culturing. In comparison, nucleic acid amplification testing (NAAT) provides superior sensitivity and specificity and is now the recommended method for diagnosis in most cases.(2-5) Immunoassays and nonamplification DNA tests are also available for N gonorrhoeae detection, but these methods are significantly less sensitive and less specific than NAAT.(2-5) Improved screening rates and increased sensitivity of NAAT testing have resulted in an increased number of accurately diagnosed cases.(2-5) Improved detection rates result from both the increased performance of the assay and the patients' easy acceptance of urine testing. Early identification of infection enables sexual partners to seek testing and/or treatment as soon as possible and reduces the risk of disease spread. Prompt treatment reduces the risk of infertility in women.

Useful For: Detection of Neisseria gonorrhoeae for non-FDA approved specimen types

Interpretation: A positive result indicates the presence of rRNA of Neisseria gonorrhoeae. A negative result indicates that rRNA for N gonorrhoeae was not detected in the specimen. The predictive value of an assay depends on the prevalence of the disease in any particular population. In settings with a high prevalence of sexually transmitted disease, positive assay results have a high likelihood of being true positives. In settings with a low prevalence of sexually transmitted disease, or in any settings in which a patient's clinical signs and symptoms or risk factors are inconsistent with gonococcal or chlamydial urogenital infection, positive results should be carefully assessed and the patient retested by other methods (eg, culture for N gonorrhoeae), if appropriate.

Reference Values:

Negative

Neisseria Meningitidis IgG Vaccine Response

Reference Values:
Reference Ranges (pre-vaccination):

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<tr>
<th>Serogroup</th>
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<tr>
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</tr>
<tr>
<td>Serogroup C</td>
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<tr>
<td>Serogroup Y</td>
<td>&lt;4.0 ug/mL</td>
</tr>
<tr>
<td>Serogroup W-135</td>
<td>&lt;3.0 ug/mL</td>
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</tbody>
</table>

This assay measures serum IgG antibodies recognizing polysaccharide antigens from the four Neisseria meningitidis serogroups included in the licensed meningococcal vaccine. The meningococcal vaccine response is best evaluated by testing pre-vaccination and post-vaccination samples in parallel. A two-fold or greater increase for at least two sero-groups is expected when comparing post-vaccination to pre-vaccination results. N. meningitidis IgG levels peak approximately one month post-vaccination, but decline markedly by two years.

Neonatal Bilirubin, Serum

Clinical Information: Bilirubin is one of the most commonly used tests to assess liver function. Approximately 85% of the total bilirubin produced is derived from the heme moiety of hemoglobin, while the remaining 15% is produced from RBC precursors destroyed in the bone marrow and from the catabolism of other heme-containing proteins. After production in peripheral tissues, bilirubin is rapidly taken up by hepatocytes where it is conjugated with glucuronic acid to produce bilirubin mono- and diglucuronide, which are then excreted in the bile. A number of inherited and acquired diseases affect one or more of the steps involved in the production, uptake, storage, metabolism, and excretion of bilirubin. Bilirubinemia is frequently a direct result of these disturbances. The most commonly occurring form of unconjugated hyperbilirubinemia is that seen in newborns and referred to as physiological jaundice. The increased production of bilirubin, that accompanies the premature breakdown of erythrocytes and ineffective erythropoiesis, results in hyperbilirubinemia in the absence of any liver abnormality. The rare genetic disorders, Crigler-Najjar syndromes type I and type II, are caused by a low or absent activity of bilirubin UDP-glucuronyl-transferase. In type I, the enzyme activity is totally absent, the excretion rate of bilirubin is greatly reduced and the serum concentration of unconjugated bilirubin is greatly increased. Patients with this disease may die in infancy owing to the development of kernicterus. In hepatobiliary diseases of various causes, bilirubin uptake, storage, and excretion are impaired to varying degrees. Thus, both conjugated and unconjugated bilirubin are retained and a wide range of abnormal serum concentrations of each form of bilirubin may be observed. Both conjugated and unconjugated bilirubins are increased in hepatitis and space-occupying lesions of the liver; and obstructive lesions such as carcinoma of the head of the pancreas, common bile duct, or ampulla of Vater.

Useful For: Assessing liver function Evaluating a wide range of diseases affecting the production, uptake, storage, metabolism, or excretion of bilirubin Monitoring the efficacy of neonatal phototherapy
Interpretation: The level of bilirubinemia that results in kernicterus in a given infant is unknown. In preterm infants, the risk of a handicap increases by 30% for each 2.9 mg/dL increase of maximal total bilirubin concentration. While central nervous system damage is rare when total serum bilirubin (TSB) is <20 mg/dL, premature infants may be affected at lower levels. The decision to institute therapy is based on a number of factors including TSB, age, clinical history, physical examination, and coexisting conditions. Phototherapy typically is discontinued when TSB level reaches 14 to 15 mg/dL. Physiologic jaundice should resolve in 5 to 10 days in full-term infants and by 14 days in preterm infants. When any portion of the biliary tree becomes blocked, bilirubin levels will increase.

Reference Values:
DIRECT
> or =12 months: 0.0-0.3 mg/dL
Reference values have not been established for patients who are <12 months of age.

TOTAL
0-6 days: Refer to www.bilitool.org for information on age-specific (postnatal hour of life) serum bilirubin values. 7-14 days: <15.0 mg/dL
15 days to 17 years: < or =1.0 mg/dL
> or =18 years: < or =1.2 mg/dL


Nettle, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49  Positive
3 3.50-17.4  Positive
4 17.5-49.9  Strongly positive
5 50.0-99.9  Strongly positive
6 > or =100  Strongly positive Reference values apply to all ages.


Neu-N Immunostain, Technical Component Only

Clinical Information: Neuronal-nuclei (Neu-N) protein is expressed in neurons in the brain and ganglia in the peripheral nervous system. Presence of Neu-N has been correlated with the withdrawal of the neuron from the cell cycle and with terminal differentiation of the neuron

Useful For: Identification of neuronal nuclei

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Neuraminidase, Fibroblasts

Clinical Information: Sialidosis, also known as mucolipidosis I, is an autosomal recessive lysosomal storage disorder (LSD) resulting from an isolated deficiency of the enzyme neuraminidase. Clinical presentation can vary and phenotypes are typically categorized by age of onset. Type I is considered to be the milder form of sialidosis and is characterized by a cherry-red spot on the retina, progressive decreased acuity, impaired color vision, or night blindness. Neurologic problems include gait abnormalities and poorly controlled myoclonus. Type II sialidosis is distinguished from type I by the presence of dysmorphic features, including coarse facies, hepatosplenomegaly, and dysostosis multiplex, early age of onset, and its more rapid disease progression. Developmental delay is frequently present in type II sialidosis. The congenital form is typically associated with hydrops. Galactosialidosis is an autosomal recessive lysosomal storage disease associated with a combined deficiency of neuraminidase and beta-galactosidase secondary to a defect in the cathepsin A protein. Clinical features are those typically associated with LSD including coarse facial features, cherry-red spots, and skeletal dysplasia. The disorder can be classified into 3 subtypes that vary with respect to age of onset and
clinical presentation. The early infantile form is associated with fetal hydrops, visceromegaly, skeletal and ophthalmologic disorders, and early death. The late infantile form typically presents with short stature, dysostosis multiplex, coarse facial features, hepatosplenomegaly, and heart valve problems. The juvenile/adult form is characterized by progressive neurologic degeneration, ataxia, cognitive disability, and angiokeratomas. Most of the juvenile/adult onset cases have been found in individuals of Japanese ancestry. A diagnosis of galactosialidosis is obtained by demonstrating a combined deficiency of neuraminidase and beta-galactosidase in lymphocytes or cultured skin fibroblasts.

**Useful For:** Aids in the diagnosis of sialidosis and galactosialidosis

**Interpretation:** Specimens with activity more than 0.10 nmol/min/mg protein are considered to be normal. Specimens with activity of 0.10 nmol/min/mg protein or less are considered to be abnormal and suggestive of neuraminidase deficiency. Molecular confirmation is recommended.

**Reference Values:** >0.10 nmol/min/mg Prot


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**NONCP 603047**

**Neuro-Oncology Expanded Panel with Rearrangement, Tumor**

**Clinical Information:** Molecular analysis of biomarkers is increasingly being used in oncology practice to support and guide diagnosis, prognosis, and therapeutic management. Molecular profiling has been incorporated in the WHO classification of central nervous system (CNS) tumors and allows for robust delineation of diagnostic groups characterized by distinct molecular profiles with superior prognostic significance than histopathological classification alone. This test interrogates targeted regions across 219 genes associated with a variety of adult and pediatric CNS tumors to assess for the presence of somatic mutations and rearrangements, including mutations in IDH1/2, TERT, ATRX, TP53, H3F3A, HIST1H3B/C, BRAF, SMARCB1, and SMARCA4, and rearrangements involving RELA, BRAF, and EGFR (eg, EGFR vIII). See Targeted Gene Regions Interrogated by Neuro-Oncology Panel in Special Instructions for details regarding the targeted gene regions identified by this test.

**Useful For:** Identifying mutations and rearrangements that may support a diagnosis for patients with tumors of the central nervous system (CNS) Identifying mutations and rearrangements that may help determine prognosis for patients with tumors of the CNS Identifying specific mutations and rearrangements within genes known to be associated with response or resistance to specific cancer therapies

**Interpretation:** An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided.

Neuroblastoma, 2p24 (MYCN) Amplification, FISH

Clinical Information: Neuroblastoma is a solid tumor that occurs in early childhood and is usually found in the adrenal glands, but rarely is found in other areas of the body. Approximately 25% of all neuroblastomas have amplification of the MYCN oncogene, located on chromosome 2 at p24.1. Amplification of the MYCN oncogene correlates with an unfavorable prognosis and aggressive disease. This test is not diagnostic for neuroblastoma. Other tumors including medulloblastoma, retinoblastoma, astrocytoma, and small cell lung cancer may have amplification of MYCN.

Useful For: As a prognostic factor for patients with neuroblastoma As an aid to treatment decisions in some patients with neuroblastoma

Interpretation: MYCN gene amplification is detected when the percent of cells with an abnormality exceeds the normal cutoff for the MYCN probe. A positive result is consistent with MYCN gene amplification. A negative result suggests no MYCN gene amplification. However, this result does not exclude the diagnosis of neuroblastoma.

Reference Values: An interpretive report will be provided.

Chromosome 2 at p24. Amplification of the MYCN oncogene correlates with an unfavorable prognosis and aggressive disease. Since metastasis to the bone marrow is common, detection of MYCN amplification in tumor cells present in the bone marrow is important. Prior to ordering this bone marrow test, if possible, testing on the primary tumor sample should be performed. If the primary tumor tests negative for MYCN amplification, bone marrow testing is not indicated. If the primary tumor demonstrates MYCN amplification, identification of MYCN amplification in the bone marrow will confirm the presence of metastatic disease. In some cases, the diagnostic biopsy specimen from the primary tumor is small and insufficient specimen may be available for ancillary tests such as FISH. In addition, if the primary sample is a bone biopsy, it cannot be used for FISH analysis. In such cases, if metastatic disease involving the bone marrow is identified, FISH testing on the bone marrow can be performed to evaluate for MYCN status in the tumor.

**Useful For:** Aids in identifying metastatic disease in patients with a neuroblastoma that has been previously determined to be positive for the MYCN oncogene

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for any given probe. The presence of a positive clone supports a diagnosis of metastatic disease. The absence of an abnormal clone does not rule out the presence of metastatic disease.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**NF2F 70520**

**Neurofilament (2F11)(NF 2F11) Immunostain, Technical Component Only**

**Clinical Information:** Neurofilament (NF) constitutes the main structural elements of neuronal axons and dendrites. NF subunits are present in neurons, neuronal processes, peripheral nerves, and sympathetic ganglion cells. In brain tissue, immunoperoxidase staining for NF labels the cytoplasm in the body of neurons and also labels neuronal processes. Within tumors, only neoplastic cells of neural origin or those exhibiting neuronal differentiation have been observed to express NF. Positive immunostaining has been observed in neuromas, gangliogliomas, neuroblastomas, and medulloblastomas. Other tumors that can stain for NF include pheochromocytoma, chemodectomas, and carcinoid tumors.

**Useful For:** Aids in the identification of neoplastic cells of neural origin or those exhibiting neuronal differentiation

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
Neurofilament (SMI31) Immunostain, Technical Component Only

Clinical Information: Neurofilament antibody clone SMI 31 reacts with a phosphorylated epitope on neurofilament H and, to a lesser degree, neurofilament M. Both of these proteins contain multiple tandemly repeated serine phosphorylation sites. Clone SMI 31 reacts with thick and thin axons and specific dendrites such as basket cell dendrites. SMI 31 may also stain neuronal cell bodies in pathological conditions.

Useful For: Differentiating neurons (NF+) from glia (NF-)

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

Neuroimmunology Antibody Follow-up, Serum

Clinical Information: Paraneoplastic autoimmune neurological disorders reflect a patient's humoral and cellular immune responses to cancer. The cancer may be new or recurrent, is usually limited in metastatic volume, and is often occult by standard imaging procedures. Autoantibodies specific for onconeural proteins found in the plasma membrane, cytoplasm, and nucleus of neurons or muscle are generated in this immune response and serve as serological markers of paraneoplastic autoimmunity. The most commonly recognized cancers in this context are small-cell lung carcinoma (SCLC), thymoma, ovarian (or related mullerian) carcinoma, breast carcinoma, and Hodgkin's lymphoma. Pertinent childhood neoplasms recognized thus far include neuroblastoma, thymoma, Hodgkin's lymphoma, and chondroblastoma. An individual patient's autoantibody profile can predict a specific neoplasm with 90% certainty, but not the neurological syndrome. Four classes of autoantibodies are recognized: -Neuronal nuclear (antineuronal nuclear antibody-type 1 [ANNA-1], ANNA-2, ANNA-3) -Neuronal and muscle cytoplasmic (Purkinje cell cytoplasmic antibody, type 1 [PCA-1], PCA-2, PCA-Tr, CRMP-5, amphiphysin, and striational) -Glial nuclear (anti-gial nuclear antibody) -Plasma membrane cation channel Antibodies (neuronal P/Q-type and N-type calcium channel and muscle acetylcholine receptor autoantibodies). These autoantibodies are potential effectors of neurological dysfunction. Seropositive patients usually present with subacute neurological symptoms and signs. The patient may present with encephalopathy, cerebellar ataxia, myelopathy, radiculopathy, plexopathy, sensory, sensorimotor, or autonomic neuropathy, with or without coexisting evidence of a neuromuscular transmission disorder: Lambert-Eaton syndrome (LES), myasthenia gravis, or neuromuscular hyperexcitability. Initial signs may be subtle, but a subacute multifocal and progressive syndrome usually evolves. Sensorimotor neuropathy and cerebellar ataxia are common presentations,
but the clinical picture in some patients is dominated by striking gastrointestinal dysmotility, limbic encephalopathy, basal ganglionitis, or cranial neuropathy (especially loss of vision, hearing, smell, or taste). Cancer risk factors include past or family history of cancer, history of smoking or social/environmental exposure to carcinogens. Early diagnosis and treatment of the neoplasm favors less neurological morbidity and offers the best hope for survival.

**Useful For:** Monitoring patients who have previously tested positive for 1 or more antibodies in the Mayo Neuroimmunology Laboratory within the past 5 years. Requests for the follow-up assay in serum specimens must have previously been positive in a serum evaluation.

**Interpretation:** Antibodies directed at onconeural proteins shared by neurons, muscle, and certain cancers are valuable serological markers of a patient's immune response to cancer. They are not found in healthy subjects and are usually accompanied by subacute neurological symptoms and signs. Several autoantibodies have a syndromic association, but no known autoantibody predicts a specific neurological syndrome. Conversely, a positive autoantibody profile has 80% to 90% predictive value for a specific cancer. It is not uncommon for more than 1 paraneoplastic autoantibody to be detected, each predictive of the same cancer.

**Reference Values:**

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<tr>
<td>PCATR</td>
<td>Purkinje Cell Cytoplasmic Ab Type Tr</td>
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**Clinical References:** Lancaster E, Martinez-Hernandez E, Dalmau J: Encephalitis and antibodies to
Neuroimmunology Antibody Follow-up, Spinal Fluid

Clinical Information: Paraneoplastic autoimmune neurological disorders reflect a patient's humoral and cellular immune responses to cancer. The cancer may be new or recurrent, is usually limited in metastatic volume, and is often occult by standard imaging procedures. Autoantibodies specific for onconeural proteins found in the plasma membrane, cytoplasm, and nucleus of neurons or muscle are generated in this immune response, and serve as serological markers of paraneoplastic autoimmunity. The most commonly recognized cancers in this context are small-cell lung carcinoma (SCLC), thymoma, ovarian (or related mullerian) carcinoma, breast carcinoma, and Hodgkin's lymphoma. Pertinent childhood neoplasms recognized thus far include neuroblastoma, thymoma, Hodgkin's lymphoma, and chondroblastoma. An individual patient's autoantibody profile can predict a specific neoplasm with 90% certainty, but not the neurological syndrome. Three classes of autoantibodies are recognized in the spinal fluid analysis: -Neuronal nuclear (antineuronal nuclear antibody-type 1 [ANNA-1], ANNA-2, ANNA-3) -Neuronal and muscle cytoplasmic (Purkinje cell cytoplasmic antibody, type 1 [PCA-1]; PCA-2; PCA-Tr, CRMP-5, and amphiphysin) -Gliarial nuclear (anti-gliarial nuclear antibody: AGNA) Seropositive patients usually present with subacute neurological symptoms and signs. The patient may present with encephalopathy, cerebellar ataxia, myelopathy, radiculopathy, plexopathy, sensory, sensorimotor, or autonomic neuropathy, with or without coexisting evidence of a neuromuscular transmission disorder: Lambert-Eaton syndrome (LES), myasthenia gravis, or neuromuscular hyperexcitability. Initial signs may be subtle, but a subacute multifocal and progressive syndrome usually evolves. Sensorimotor neuropathy and cerebellar ataxia are common presentations, but the clinical picture in some patients is dominated by striking gastrointestinal dysmotility, limbic encephalopathy, basal ganglionitis, or cranial neuropathy (especially loss of vision, hearing, smell, or taste). Cancer risk factors include past or family history of cancer, history of smoking, or social/environmental exposure to carcinogens. Early diagnosis and treatment of the neoplasm favor less neurological morbidity and offer the best hope for survival. Requests for this follow-up assay in spinal fluid specimens can only be performed when patients have previously been positive in a spinal fluid evaluation.

Useful For: Monitoring patients who have previously tested positive for 1 or more antibodies within the past 5 years in a Mayo Clinic Neuroimmunology Laboratory evaluation

Interpretation: Antibodies directed at onconeural proteins shared by neurons, muscle, and certain cancers are valuable serological markers of a patient's immune response to cancer. They are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. Several autoantibodies have a syndromic association, but no known autoantibody predicts a specific neurological syndrome. Conversely, a positive autoantibody profile has 80% to 90% predictive value for a specific cancer. It is not uncommon for more than 1 paraneoplastic autoantibodies to be detected, each predictive of the same cancer.

Reference Values:

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<th>Reference Value</th>
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<td>ANN1C</td>
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<td>CASPR2-IgG CBA, CSF</td>
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<tr>
<td>Assay</td>
<td>Description</td>
<td>CSF Result</td>
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<tr>
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<td>------------------------------------------------------------------------------</td>
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<td>NMO/AQP4 FACS Titer, CSF</td>
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<td>Paraneoplastic Autoantibody WBlot, CSF Negative</td>
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**Clinical References:** Lancaster E, Martinez-Hernandez E, Dalmau J: Encephalitis and antibodies to synaptic and neuronal cell surface proteins. Neurology 2011;77(2):179-189

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**NEEVP 84162 Neurologic Enzyme Evaluation**

**Clinical Information:** Several RBC enzymes are known to cause a nonspherocytic hemolytic anemia (HA). The most common cause of these are glucose-6-phosphate dehydrogenase and pyruvate kinase deficiency. Four other RBC enzymes that cause HA have also been associated with hereditary myopathic or neurologic disorders. These enzymes are phosphofructokinase, triosephosphate isomerase, phosphoglycerate kinase, and glutathione synthase. Kinetic enzyme assays are available for the first 3 disorders. Quantitative measurement of glutathione substitutes for analysis of the enzyme glutathione synthase.

**Useful For:** Evaluating patients who have a hemolytic process that is associated with some neurologic findings

**Interpretation:** Definitive results and an interpretive report will be provided. Significant abnormal values typically are 25% of values obtained for a normal individual.

**Reference Values:**

Definitive results and an interpretive report will be provided.


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**NMPAN 65434 Neuromuscular Genetic Panels by Next-Generation Sequencing (NGS)**

**Clinical Information:** Inherited neuromuscular disorders are a diverse group of diseases with heterogeneous genetic causes that affect the peripheral nervous system. The age of onset for these disorders ranges from in utero to old age. Based on the pattern of inheritance; clinical presentation; nerve conductions including, electromyography (EMG) pattern, and muscle and nerve biopsy findings; inherited neuromuscular disorders can be divided into major categories. These categories include muscular...
dystrophies, congenital muscular dystrophies, congenital myopathies, distal myopathies, ion channel hyperexcitable muscle diseases, metabolic myopathies, congenital myasthenic syndromes, hereditary motor and sensory neuropathies, hereditary motor neuropathies, motor neuron disorders, hereditary spastic paraplegias, and hereditary sensory neuropathies. Due to the considerable overlap in the clinical phenotypes of various neuromuscular disorders, it is often difficult to distinguish these specific inherited disorders from acquired forms without genetic testing. Additionally, even though most myopathies present with proximal shoulder and girdle weaknesses, some forms may present with distal weakness and, thereby, mimic neuropathies. Therefore, genetic testing can be extremely helpful in making the diagnosis. This is especially true for some genetic forms where neurophysiology may be ambiguous, as both neuropathy and myopathy exist simultaneously. Motor Neuron Disease (MND): MND selectively affect the motor neurons with degeneration. MND include 1) primary lateral sclerosis (PLS), 2) primary muscular atrophy (PMA), and 3) amyotrophic lateral sclerosis (ALS). In PLS and PMA, the motor neuron degeneration is limited to the upper motor neuron and lower motor neuron, respectively. The clinical phenotype of PLS can include gradual progressive leg weakness and spasticity and spastic bulbar weakness. In ALS, the most frequent form of MND, degeneration involves both upper and lower motor neurons and results in progressive muscle weakness, paralysis, and death from respiratory failure, usually within 3 to 5 years of disease onset. Muscular Dystrophy: Muscular dystrophies are characterized by skeletal muscle wasting. The muscular dystrophies can be subdivided into the dystrophinopathies, Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophies, distal myopathies, and congenital muscular dystrophies. A clinical diagnosis is typically based on distribution and severity of muscular involvement, mode of inheritance, and other associated symptoms. The dystrophinopathies include Duchenne muscular dystrophy and Becker muscular dystrophy. These 2 forms are inherited in an X-linked manner and typically present with variable degrees of a limb-girdle pattern of weakness and can develop dilated cardiomyopathy. Limb-girdle muscular dystrophy is characterized by weakness and wasting predominately of the hips, shoulders, and proximal extremity muscles. Congenital muscular dystrophies are progressive early-onset muscle disorders that often have brain and other organ involvement. They are characterized by hypotonia, delayed motor development, and progressive weakness. Emery-Dreifuss Muscular Dystrophy: Emery-Dreifuss muscular dystrophy is characterized by the triad of joint contractures, slowly progressive muscle weakness and wasting, and cardiac involvement. Joint contractures usually being in early childhood and predominate in the elbows, ankles, and postcervical muscles. Age of onset, progression, and severity of disease demonstrate inter- and intrafamilial variability. Distal Myopathy: Distal myopathies are characterized by distal weakness and atrophy that starts in the muscles of the hands or feet and lack of cranial involvement or sensory loss. Distal myopathies are classified based on clinical features, inheritance pattern, and histopathological findings, such as the presence of rimmed vacuoles. Categories of distal myopathies include late adult-onset autosomal dominant forms, adult-onset autosomal dominant forms, early-onset autosomal dominant forms, early-onset autosomal recessive forms, and early adult-onset autosomal recessive forms. Additionally, inclusion body myositis presents with distal muscle weakness and may be in the differential with the distal myopathies. Myofibrillar Myopathy: Myofibrillar myopathies are characterized by slowly progressive weakness involving the proximal and distal muscles. The clinical phenotype can include peripheral neuropathy, cardiomyopathy, muscle stiffness, aching and cramps. While myofibrillar myopathies are typically adult onset disorders, individuals can present anywhere from early childhood through adulthood. Congenital Myopathy: Congenital myopathies are characterized by early-onset and specific histopathologic abnormalities on muscle biopsy. The clinical phenotype can include congenital hypotonia, generalized muscle weakness, delayed motor milestones, feeding difficulties, and facial muscle involvement. While congenital myopathies typically occur in childhood, individuals do occasionally present in adulthood. Also, individuals typically have slow progressive weakness, but in some cases the course may be severe. Congenital Myasthenic Syndrome: Congenital myasthenic syndromes are characterized by fatigable weakness involving oculocutaneous and limb muscles. The severity and disease course is highly variable, but individuals usually present in infancy or early childhood. The clinical phenotype associated with a neonatal onset can include feeding difficulties, poor suck and cry, choking spells, eyelid ptosis, and muscle weakness. The clinical phenotype associated with a later childhood onset can include abnormal muscle fatigue, delayed motor milestones, ptosis, and extracocular muscle weakness. Metabolic Myopathy: Metabolic myopathies are a diverse group of inherited biochemical diseases involving limitation of the use of fuels by skeletal muscle to generate energy. These diseases can be categorized as disorders of lipid metabolism, glycogen and glucose metabolism, or mitochondrial myopathies that impair both lipid and glucose metabolism. Biochemical testing in multiple tissue types including blood, urine, and muscle, can help to determine which category of muscle disease is most likely.
Disorders of fatty acid oxidation (FAO) are one category of metabolic myopathies characterized by hypoketotic hypoglycemia, hepatic dysfunction, skeletal myopathy, dilated and hypertrophic cardiomyopathy, and sudden or unexpected death. Mitochondrial fatty acid beta-oxidation plays an important role in energy production, particularly in skeletal and heart muscle, and in hepatic ketone body formation during periods of fasting. Biochemical testing such as urine organic acids, plasma acylcarnitines, and fatty acids can aid in diagnosis. These test results are influenced by dietary factors and the clinical status of the patient, however, which often leads to incomplete diagnostic information or even false-negative results. Disorders of glycogen and glucose metabolism are another category of metabolic myopathies primarily affecting muscle and resulting in exercise intolerance, recurrent rhabdomyolysis, and myoglobinuria. Creatine kinase level is typically elevated during a major event. Muscle biopsy is often performed to verify absence of enzyme activity for the specific type of glycogenosis disease. Polyglucosan body disease involves progressive neurogenic bladder, spasticity and weakness causing gait difficulties from either primary muscle or nerve involvements, sensory loss mainly in the distal lower extremities, and mild cognitive difficulties such as executive dysfunction. Mitochondrial myopathy due to coenzyme Q10 (CoQ10) deficiency is a group of heterogeneous diseases. These mitochondrial diseases are characterized by muscle weakness, exercise intolerance, elevated creatine kinase, and abnormal muscle biopsy findings. Skeletal Muscle Channelopathy: Nondystrophic myotonias are characterized by muscle stiffness generated by voluntary movement. Other features included transient or prolonged weakness, pain associated with myotonia, and fatigue. The nondystrophic myotonias include myotonia congenita, paramyotonia congenital, and sodium channel myotonia. The periodic paralyses are characterized by episodic attacks of weakness often triggered by diet or rest after exercise. They include hyperkalemic periodic paralysis, hypokalemic periodic paralysis, and Andersen-Tawil syndrome. Rhabdomyolysis: Rhabdomyolysis results from the rapid breakdown of skeletal muscle fibers, which lead to leakage of potentially toxic cellular contents into the blood stream. The clinical severity can range from asymptomatic creatine kinase elevation to a life-threatening disease. The clinical features include acute-onset myalgia, transient muscle weakness, and pigmenturia. Genetic causes of rhabdomyolysis include metabolic muscle disorders, mitochondrial disorders, disorders of intramuscular calcium release and excitation-coupling, and muscular dystrophies.

**Useful For:** Establishing a diagnosis of a neuromuscular disorder associated with known causal genes Serving as a second-tier test for patients in whom previous targeted gene mutation analyses for specific inherited neuromuscular disorder-related genes were negative Identifying mutations within genes known to be associated with inherited neuromuscular disorders, allowing for predictive testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

Neuromyelitis Optica (NMO)/Aquaporin-4-IgG Fluorescence-Activated Cell Sorting (FACS) Assay, Serum

Clinical Information: Neuromyelitis optica (NMO), sometimes called Devic disease or opticospinal multiple sclerosis (MS) is a severe, relapsing, autoimmune, inflammatory and demyelinating central nervous system disease that predominantly affects optic nerves and spinal cord.(1) The disorder is now recognized as a spectrum of autoimmunity (termed NMO spectrum disorders [NMOSD]) targeting the astrocytic water channel aquaporin-4 (AQP4).(1,2) Brain lesions are observed in >60% of patients with NMOSD and approximately 10% will be MS-like.(3) Children tend to have greater brain involvement than adults and brain lesions are more symptomatic than is typical for adult patients.(4) Extensive cerebral white matter signal abnormalities are sometimes encountered, most commonly in children, and are sometimes associated with encephalopathy. Circumventricular organs (CVO; eg, area postrema) are preferentially involved. Symptoms and signs attributable to area postrema involvement include intractable hiccups, nausea and vomiting, and these may occur in isolation, herald the onset of NMO or occur in association with the more classical optic neuritis or Longitudinally Extensive Transverse Myelitis (LETM).(5) Magnetic resonance imaging typically reveals large inflammatory spinal cord lesions involving 3 or more vertebral segments. During acute attacks, the cerebrospinal fluid contains inflammatory cells, but usually lacks evidence of intrathecal IgG synthesis. The clinical course is characterized by relapses of optic neuritis or transverse myelitis, or both. Many patients with NMOSD are misdiagnosed as having MS. Importantly, the prognosis and optimal treatments for the 2 diseases differ. NMOSD typically has a worse natural history than MS, with frequent and early relapses. NMOSD attacks are often severe resulting in a rapid accumulation of disability (blindness and paraplegia). More effective treatments combined with earlier and more accurate diagnosis has led to improved outcomes. Currently, in the AQP4-IgG era, 5 years after onset, approximately 30% of NMO patients will require a cane to walk and 10% will be wheelchair bound. Treatments for NMOSD include corticosteroids and plasmapheresis for acute attacks and mycophenolate mofetil, azathioprine, and rituximab for relapse prevention. Beta-interferon, a treatment promoted for MS, exacerbates NMOSD. Therefore, early diagnosis and initiation of NMO-appropriate immunosuppressant treatment is important to optimize the clinical outcome by preventing further attacks. Skeletal muscle abnormalities with hyperCKemia have been reported in a few NMOSD patients. Recent reports indicate focal retinal vascular attenuation, inner nuclear layer thickening and microcystic edema in some NMO patients. The sensitivity and specificity of Fluorescence-Activated Cell Sorting (FACS) assay for NMO is >80% and >99%, respectively. Detection of NMO/APQ4-IgG allows distinction of NMOSD from MS and is indicative of a relapsing disease, mandating initiation of immunosuppression, even after the first attack, thereby reducing attack frequency and disability in the future.

Useful For: Diagnosis of a neuromyelitis optica spectrum disorder (NMOSD) Diagnosis of autoimmune AQP4 channelopathy Diagnosis of neuromyelitis optica (NMO) Distinguishing NMOSD from multiple sclerosis early in the course of disease

Interpretation: A positive value is consistent with a neuromyelitis optica spectrum disorder (NMOSD) and justifies initiation of appropriate immunosuppressive therapy at the earliest possible time. This allows early initiation and maintenance of optimal therapy. Recommend follow-up in 3 to 6 months if NMOSD is suspected. This autoantibody is not found in healthy subjects.

Reference Values:
Negative


Neuromyelitis Optica (NMO)/Aquaporin-4-IgG Fluorescence-Activated Cell Sorting (FACS) Assay, Spinal Fluid

Clinical Information: Neuromyelitis optica (NMO), sometimes called Devic disease or opticospinal multiple sclerosis (MS) is a severe, relapsing, autoimmune, inflammatory and demyelinating central nervous system disease that predominantly affects optic nerves and spinal cord. The disorder is now recognized as a spectrum of autoimmunity (termed NMO spectrum disorders: NMOSD) targeting the astrocytic water channel aquaporin-4 (AQP4). Brain lesions are observed in >60% of patients with NMOSD and approximately 10% will be MS-like. Children tend to have greater brain involvement than adults and brain lesions are more symptomatic than is typical for adult patients. Extensive cerebral white matter signal abnormalities are sometimes encountered, most commonly in children, and are sometimes associated with encephalopathy. Circumventricular organs (CVO; e.g., area postrema) are preferentially involved. Symptoms and signs attributable to area postrema involvement include intractable hiccups, nausea and vomiting, and these may occur in isolation, herald the onset of NMO, or occur in association with the more classical optic neuritis or Longitudinally Extensive Transverse Myelitis (LETM). Magnetic resonance imaging typically reveals large inflammatory spinal cord lesions involving 3 or more vertebral segments. During acute attacks, the cerebrospinal fluid contains inflammatory cells, but usually lacks evidence of intrathecal IgG synthesis. The clinical course is characterized by relapses of optic neuritis or transverse myelitis, or both. Many patients with NMOSD are misdiagnosed as having MS. Importantly, the prognosis and optimal treatments for the 2 diseases differ. NMOSD typically has a worse natural history than MS, with frequent and early relapses. NMOSD attacks are often severe resulting in a rapid accumulation of disability (blindness and paraplegia). More effective treatments combined with earlier and more accurate diagnosis has led to improved outcomes. Currently, in the AQP4-IgG era, 5 years after onset, approximately 30% of NMO patients will require a cane to walk and 10% will be wheelchair bound. Treatments for NMOSD include corticosteroids and plasmapheresis for acute attacks and mycophenolate mofetil, azathioprine, and rituximab for relapse prevention. Beta-interferon, a treatment promoted for MS, exacerbates NMOSD. Therefore, early diagnosis and initiation of NMO-appropriate immunosuppressant treatment is important to optimize the clinical outcome by preventing further attacks. Skeletal muscle abnormalities with hyerCKemia have been reported in a few NMOSD patients. Recent reports indicate focal retinal vascular attenuation, inner nuclear layer thickening and microcystic edema in some NMO patients. Detection of AQP4-IgG by NMO/AQP4 FACS in cerebrospinal fluid (CSF) allows distinction from MS and is indicative of an NMOSD. Though serum is optimal for AQP4-IgG testing, occasionally physicians submit only CSF for testing. A previous study, based on our first-generation indirect immunofluorescence assay compared the frequencies of AQP4-IgG in serum and CSF. The positivity rate was greater for serum alone than for CSF alone. However, testing of CSF was helpful when the serum was negative. Detection of AQP4-IgG in CSF allowed unambiguous distinction of NMO from MS. CSF testing offered the additional advantage of generally lacking the nonorgan-specific IgG autoantibodies (e.g., antinuclear, antimitochondrial, and smooth muscle) that are common in serum of patients with NMO and also with classic paraneoplastic autoimmune disorders. Recent AQP4 FACS analysis of paired CSF and serum samples from 66 patients submitted for AQP4-IgG testing reveals a slightly better detection rate in serum (n=59) compared with CSF (n=55). All 7 patients who tested negative in serum also tested negative in CSF.

Useful For: Diagnosis of a neuromyelitis optica spectrum disorder (NMOSD) Diagnosis of autoimmune AQP4 channelopathy Distinguishing NMOSD from multiple sclerosis early in the course of disease

Interpretation: A positive value is consistent with a neuromyelitis optica spectrum disorder (NMOSD) and justifies initiation of appropriate immunosuppressive therapy at the earliest possible time. This allows
early initiation and maintenance of optimal therapy. This autoantibody is not found in healthy subjects.

Reference Values:

Negative


Neuron-Specific Enolase (NSE), Serum

Clinical Information: Enolase is a glycolytic enzyme that catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate. Enolase exists in the form of several tissue-specific isoenzymes, consisting of homo or heterodimers of 3 different monomer-isofoms (alpha, beta, and gamma). Neuron specific enolase (NSE) is a 78 kD gamma-homodimer and represents the dominant enolase-isoenzyme found in neuronal and neuroendocrine tissues. Its levels in other tissues, except erythrocytes, are negligible. The biological half-life of NSE in body fluids is approximately 24 hours. Due to this organ-specificity, concentrations of NSE in serum or, more commonly, cerebrospinal fluid (CSF), are often elevated in diseases which result in relative rapid (hours/days to weeks, rather than months to years) neuronal destruction. Measurement of NSE in serum of CSF can therefore assist in the differential diagnosis of a variety of neuron-destructive and neurodegenerative disorders. The most common application is in the differential diagnosis of dementias, where elevated CSF concentrations support the diagnosis of rapidly progressive dementias, such as Creutzfeldt-Jacob Disease. NSE might also have utility as a prognostic marker in neuronal injury. There is, for example, increasing evidence that elevated serum NSE levels correlate with a poor outcome in coma, in particular when caused by hypoxic insult. NSE is also frequently overexpressed by neural crest-derived tumors. Up to 70% of patients with small cell lung carcinoma (SCLC) have elevated serum NSE concentrations at diagnosis, and approximately 90% of patients with advanced SCLC will have serum levels above the healthy reference range. Other neuroendocrine tumors with frequent expression of NSE include carcinoids (up to 66% of cases), islet cell tumors (typically <40% of cases), and neuroblastoma (exact frequency of NSE expression unknown). NSE levels in NSE-secreting neoplasms correlate with tumor mass and tumor metabolic activity. High levels have therefore some negative prognostic value. Falling or rising levels are often correlated with tumor shrinkage or recurrence, respectively.

Useful For: A follow-up marker in patients with neuron-specific enolase-secreting tumors of any type An auxiliary test in the diagnosis of small cell lung carcinoma An auxiliary test in the diagnosis of carcinoids, islet cell tumors and neuroblastomas An auxiliary tool in the assessment of comatose patients

Interpretation: Serum neuron-specific enolase (NSE) measurement has its greatest utility in the follow-up of patients with tumors of any type that have been shown to secrete NSE. With successful treatment, serum concentrations should fall with a half-life of approximately 24 hours. Persistent NSE elevations in the absence of other possible causes (see Cautions) suggest persistent tumor. Rising levels indicate tumor spread, or in patients who had previously become NSE negative, recurrence. In the context of a patient with a lung mass, disseminated malignancy of unknown origin or symptoms suggestive of paraneoplastic disease without identifiable tumor, elevated NSE suggests an underlying small cell lung carcinoma (SCLC). In patients with suspected carcinoid, islet cell tumor, or neuroblastoma, who have no clear elevations in the primary tumor markers used to diagnose these conditions, an elevated serum NSE level supports the clinical suspicion. -Carcinoid: chromogranin A, urinary 5-hydroxyindoleacetic acid, serum/blood 5-hydroxytryptamine -Islet cell tumors: variety of peptide and amine-derived hormones, chromogranin A -Neuroblastoma: vanillylmandelic acid and

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homovanillic acid When considered alongside established outcome predictors of coma, such as Glasgow coma scale and other clinical predictors (papillary light responses, corneal reflexes, motor responses to pain, myoclonus, status epilepticus), electroencephalogram, sensory evoked potentials, measurement of serum NSE concentrations provides additional information. Elevated levels are indicative of a poor outcome. Currently, no established algorithms exist to combine serum NSE concentrations and the various other predictors into a composite score that gives clear predictive outcome information. The NSE measurement therefore needs to be considered in a qualitative or semi-quantitative fashion and carefully weighed against other predictors by a physician experienced in examining and managing coma patients.

Reference Values:
< or =15 ng/mL
Serum markers are not specific for malignancy, and values may vary by method.


NSESF 81796

Neuron-Specific Enolase (NSE), Spinal Fluid

Clinical Information: Enolase is a glycolytic enzyme that catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate. Enolase exists in the form of several tissue-specific isoenzymes, consisting of homo or heterodimers of 3 different monomer-isoforms (alpha, beta, and gamma). Neuron-specific enolase (NSE) is a 78 kD gamma-homodimer and represents the dominant enolase-isoenzyme found in neuronal and neuroendocrine tissues. Its levels in other tissues, except erythrocytes, are negligible. The biological half-life of NSE in body fluids is approximately 24 hours. Due to this organ specificity, concentrations of NSE in serum or, more commonly, cerebrospinal fluid (CSF) are often elevated in diseases which result in relative rapid (hours/days to weeks, rather than months to years) neuronal destruction. Measurement of NSE in serum or CSF can therefore assist in the differential diagnosis of a variety of neuron-destructive and neurodegenerative disorders. The most common application is in the differential diagnosis of dementias, where elevated CSF concentrations support the diagnosis of rapidly progressive dementias, such as Creutzfeldt-Jakob disease (CJD). NSE might also have utility as a prognostic marker in neuronal injury. There is, for example, increasing evidence that elevated serum NSE levels correlate with a poor outcome in coma, in particular when caused by hypoxic insult.

Useful For: An auxillary test in the diagnosis of Creutzfeldt-Jakob disease An auxillary test in the diagnosis of small cell lung carcinoma metastasis to central nervous system or leptomeninges

Interpretation: The diagnosis of Creutzfeldt-Jakob disease (CJD) is highly complex and involves clinical history and neurologic examination, detection of characteristic periodic sharp and slow wave complexes on electroencephalographs, magnetic resonance imaging (hyperintense basal ganglia), and exclusion of other possible causes of dementia, in addition to cerebrospinal fluid (CSF) examination. Consequently, patients are often diagnosed as having possible, probable, or definite CJD based upon the constellation of clinical findings. Detection of elevated CSF levels of NSE protein in these patients assists in the final diagnosis. A CSF neuron-specific enolase (NSE) within the normal reference range makes sporadic CJD very unlikely, but can be observed in less rapidly progressive forms of CJD, such as variant CJD related to infection with prions that cause bovine spongiform encephalopathy. With the previous Mayo Clinic-developed assay, in a group of carefully pre-selected patients with a probable diagnosis of CJD and an indeterminate or elevated NSE concentration in CSF, the respective diagnostic sensitivities of approximately 87% and approximately 80%, and diagnostic specificities of approximately 66% and
approximately 83% were observed. Small cell lung carcinoma central nervous system metastases, particularly if they involve the leptomeninges, will lead to, usually substantial, elevations in CSF NSE concentrations.

**Reference Values:**
- Normal: < or =15 ng/mL
- Indeterminate: 15-30 ng/mL
- Elevated: >30 ng/mL

Elevated results may indicate the need for additional work-up. Possible causes may be NSE-secreting central nervous system/leptomeningeal tumor or rapid neuronal destruction from a variety of causes. In the context of dementia, elevated results may be suggestive of Creutzfeldt-Jakob disease.

**Clinical References:**

**Neuron-Specific Enolase Immunostain, Technical Component Only**

**Clinical Information:** Neuron-specific enolase (NSE) is expressed in neuronal or neuroendocrine cells, such as neurons in the brain, ganglion cells in the wall of the gastrointestinal tract, nerves, and islet cells of the pancreas. The presence of NSE can be used to confirm neuroendocrine differentiation in tumors such as carcinoids and schwannoma.

**Useful For:** Characterization of neuroendocrine differentiation in tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**Neuronal Ceroid Lipofuscinosis (NCL, Batten Disease) Panel by Next-Generation Sequencing**
Clinical Information: Neuronal ceroid lipofuscinoses (NCLs) are a subset of lysosomal storage diseases that involve defective cellular processing of lipids. NCLs are clinically characterized by epilepsy, intellectual and motor decline, and blindness. Electron microscopy typically shows a characteristic accumulation of granular osmophilic deposits (GROD), curvilinear profiles (CVB), or fingerprint profiles (FP). Enzymatic testing may show deficiency in palmitoyl-protein thioesterase 1 (PPT1), tripeptidyl-peptidase 1 (TPP1), or cathepsin D (CTSD). Currently there are at least 14 genetically distinct forms. Age of onset and clinical features can be variable, from congenital to adult onset. NCL is typically inherited in an autosomal recessive manner, although one adult onset form (ANCL; DNAJC5 gene) has been shown to be autosomal dominant. First-tier biochemical testing is available for the 2 most common types of enzyme deficiency resulting in NCL: TPPTL / Tripeptidyl Peptidase 1 (TPP1) and Palmitoyl-Protein Thioesterase 1 (PPT1), Leukocytes; and TPPTF / Tripeptidyl Peptidase 1 (TPP1) and Palmitoyl-Protein Thioesterase 1 (PPT1), Fibroblasts. Note: Testing for these 15 genes is also included in LSDP / Lysosomal Storage Disease Panel by Next-Generation Sequencing. Gene Disease Name/Locus OMIM Inheritance ATP13A2 Ceroid lipofuscinosis, neuronal, 12/Kufor-Rakeb syndrome 606693 AR CLN3 Ceroid lipofuscinosis, neuronal, 3 204200 AR CLN5 Ceroid lipofuscinosis, neuronal, 5 256731 AR CLN6 Ceroid lipofuscinosis, neuronal, 6 601780 AR CLN8 Ceroid lipofuscinosis, neuronal, 8 600143 AR CTSD Ceroid lipofuscinosis, neuronal, 10 610127 AR CTSF Ceroid lipofuscinosis, neuronal, 13, Kufs type 615362 AR CTSK Pycnodysostosis 265800 AR DNAJC5 Ceroid lipofuscinosis, neuronal, 4, Parry type 162350 AD/AR GRN Ceroid lipofuscinosis, neuronal, 11 614706 AR KCTD7 Ceroid lipofuscinosis, neuronal, 14 611726 AR MFSD8 Ceroid lipofuscinosis, neuronal, 7 610951 AR PANK2 HARP syndrome 606157 AR PPT1 Ceroid lipofuscinosis, neuronal, 1 256730 AR TPP1 Ceroid lipofuscinosis, neuronal, 2 204500 AR =autosomal recessive AD=autosomal dominant

Useful For: Follow up for abnormal biochemical or electron microscopy results suspicious for neuronal ceroid lipofuscinoses (NCLs) Identifying mutations within genes known to be associated with NCL, allowing for predictive testing of at-risk family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values: An interpretive report will be provided.


FNEUR 90156

Neurotensin

Clinical Information: Neurotensin is a 13 amino acid peptide produced primarily by endocrine cells of the ileal mucosa. Physiological actions of Neurotensin include hypertension, vasodilation, hyperglycemia, and inhibition of gastric motility. Its C-terminus is similar to Angiotensin I. It is a potent analgesic affecting hypothermia, muscle relaxation, and decreased motor activity. Pancreatic Polypeptide secretion is strongly stimulated by Neurotensin. Neurotensin appears to cause the release of Luteinizing Hormone-Releasing Hormone and Corticotropin Releasing Hormone effecting the release of Luteinizing Hormone, Follicle Stimulating Hormone, and ACTH but not Thyroid Stimulating Hormone or Growth
Hormone. Neurotensin also stimulates pancreatic bicarbonate and intestinal secretion. Neurotensin levels are stimulated by food and Bombesin. Elevated levels have been found in pancreatic endocrine tumors, Oat Cell, Squamous, and Adeno Carcinomas. Elevated levels have been found to cause watery diarrhea.

**Reference Values:**
50 - 100 pg/mL

**Neurotransmitter Metabolites (5HIAA, HVA, 3OMD) (CSF)**

**Clinical Information:** CSF Neurotransmitter Metabolites (5HIAA, HVA, 3OMD) (NC04) is useful for diagnosis of certain disorders of neurotransmitter metabolism. This testing may also be used for assessment of Variants of Uncertain Significance (VUS) identified during genetic testing (e.g. Next Generation Sequencing or Capillary Sequencing Testing). CLINICAL Monoamine metabolite testing includes homovanillic acid (HVA), 3-O-methyl-Dopa (3-OMD), and 5-hydroxyindole acetic acid (5-HIAA). This test is useful in diagnosing pediatric neurotransmitter diseases affecting dopamine and serotonin metabolism in the brain. Inborn errors of metabolism and various drugs may lead to severe imbalances and disturbances in these neurotransmitter systems that are reflected by changes in the concentration of monoamines metabolites in CSF. Primary inherited defects involve deficiencies in tyrosine and tryptophan hydroxylase, aromatic amino acid decarboxylase, monoamine oxidase, dopamine beta hydroxylase and the dopamine transporter. Other defects in the biopterin synthesis pathway may also affect dopamine and serotonin metabolism. These disorders are characterized by a wide range of symptoms that may include developmental delay, mental disability, behavioral disturbances, dystonia, seizures, encephalopathy, athetosis and ptosis.

**Interpretation:**

**Reference Values:**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>5HIAA (nmol/L)</th>
<th>HVA (nmol/L)</th>
<th>3-O-MD (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.2</td>
<td>208-1159</td>
<td>337-1299</td>
<td>&lt;300</td>
</tr>
<tr>
<td>0.2-0.5</td>
<td>179-711</td>
<td>450-1132</td>
<td>&lt;300</td>
</tr>
<tr>
<td>0.5-2.0</td>
<td>129-520</td>
<td>294-1115</td>
<td>&lt;300</td>
</tr>
<tr>
<td>2.0-5.0</td>
<td>74-345</td>
<td>233-928</td>
<td>&lt;150</td>
</tr>
<tr>
<td>5.0-10</td>
<td>66-338</td>
<td>218-852</td>
<td>&lt;100</td>
</tr>
<tr>
<td>10-15</td>
<td>67-189</td>
<td>167-563</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Adults</td>
<td>67-140</td>
<td>145-324</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>

Interpretation performed by Keith Hyland, Ph.D.

Note: If test results are inconsistent with the clinical presentation, please call our laboratory to discuss the case and/or submit a second sample for confirmatory testing.

DISCLAIMER required by the FDA for high complexity clinical laboratories: This test was developed and its performance characteristics determined by Medical Neurogenetics, LCC. It has not been cleared or approved by the U.S. FDA.

**Neurotransmitter Profile 3**

**Reference Values:**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>5MTHF (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.2</td>
<td>40-240</td>
</tr>
<tr>
<td>0.2-0.5</td>
<td>40-240</td>
</tr>
</tbody>
</table>
Neurotransmitter Metabolites/Amines

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>5HIAA (nmol/L)</th>
<th>HVA (nmol/L)</th>
<th>3-O-MD (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.2</td>
<td>208-1159</td>
<td>337-1299</td>
<td>&lt;300</td>
</tr>
<tr>
<td>0.2-0.5</td>
<td>179-711</td>
<td>450-1132</td>
<td>&lt;300</td>
</tr>
<tr>
<td>0.5-2.0</td>
<td>129-520</td>
<td>294-1115</td>
<td>&lt;300</td>
</tr>
<tr>
<td>2.0-5.0</td>
<td>74-345</td>
<td>233-928</td>
<td>&lt;150</td>
</tr>
<tr>
<td>5.0-10</td>
<td>66-338</td>
<td>218-852</td>
<td>&lt;100</td>
</tr>
<tr>
<td>10-15</td>
<td>67-189</td>
<td>167-563</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Adults</td>
<td>67-140</td>
<td>145-324</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>

Tetrahydrobiopterin/Neopterin Profile

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>BH4 (nmol/L)</th>
<th>Neop (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.2</td>
<td>40-105</td>
<td>7-65</td>
</tr>
<tr>
<td>0.2-0.5</td>
<td>23-98</td>
<td>7-65</td>
</tr>
<tr>
<td>0.5-2.0</td>
<td>18-58</td>
<td>7-65</td>
</tr>
<tr>
<td>2.0-5.0</td>
<td>18-50</td>
<td>7-65</td>
</tr>
<tr>
<td>5.0-10</td>
<td>9-40</td>
<td>7-40</td>
</tr>
<tr>
<td>10-15</td>
<td>9-32</td>
<td>8-33</td>
</tr>
<tr>
<td>Adults</td>
<td>10-30</td>
<td>8-28</td>
</tr>
</tbody>
</table>

Note: If test results are inconsistent with the clinical presentation, please call our laboratory to discuss the case and/or submit a second sample for confirmatory testing.

DISCLAIMER required by the FDA for high complexity clinical laboratories: HPLC testing was developed and its performance characteristics determined by Medical Neurogenetics. These HPLC tests have not been cleared or approved by the U.S. FDA.

**Newborn Aneuploidy Detection, FISH**

**Clinical Information:** Approximately half of clinically recognizable spontaneous abortions have a major chromosomal anomaly. Up to 95% of chromosomal abnormalities diagnosed prenatally involve aneuploidy (gain or loss of whole chromosome) of chromosomes 13, 18, 21, X, and Y. In liveborn infants, about 8/1,000 have a major chromosome anomaly, of which 6.5/1,000 involve aneuploidy of 1 of these 5 chromosomes. Diagnosis of chromosomal disorders can be performed by chromosome analysis of uncultured blood, standard chromosome study, and the technique utilizing FISH based on interphase cells. Standard chromosome analysis takes 3 to 10 days and analysis from uncultured newborn blood is often unsatisfactory and labor-intensive. FISH based methods facilitate rapid diagnosis of aneuploidy and may be helpful in medically urgent evaluations of newborn infants suspected to have aneuploidy of any of these chromosomes. This test does not detect chromosomal aneuploidies other than 13, 18, 21, X, and Y or any structural anomaly that does not result in gain of these chromosomes. Low levels of mosaicism involving chromosomes 13, 18, 21, X, or Y may not be detected by this assay.

**Useful For:** Screening for chromosomal aneuploidies of chromosomes 13, 18, 21, X, and Y in newborn peripheral blood specimens

**Interpretation:** An interpretive report will be provided.
Reference Values:
An interpretive report will be provided.


NBSR
65199

Newborn Screen Recommended Panel, Blood Spot

Clinical Information: Newborn screening as a public health measure was initiated in the early 1960s for the identification of infants affected with phenylketonuria (PKU). Since then, additional genetic and nongenetic conditions were included in screening programs. The goal of newborn screening is to detect diagnostic markers of selected disorders in blood spots collected from presymptomatic newborns. Early identification of affected newborns allows for early initiation of treatment to avoid mortality, morbidity, and disabilities due to these disorders. The US Secretary of Health and Human Services (HHS) recommends all programs screen for 34 core disorders (www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpanel/). These conditions are considered to fulfill 3 basic principles: -Condition is identifiable at a period of time (12-48 hours after birth) at which it would not ordinarily be clinically detected. -Test with appropriate sensitivity and specificity is available. -Demonstrated benefits of early detection, timely intervention, and efficacious treatment. The 34 core disorders comprise the Recommended Uniform Screening Panel (RUSP). Screening tests do not conclusively determine disease status, but measure analytes, which in most cases are not specific for a particular disease. This is the reason why the HHS Secretary also recognizes more than 25 additional conditions as secondary targets that do not meet all inclusion criteria, but are identified nevertheless because most of them are components of the differential diagnosis of screening results observed in core conditions. Even for the secondary conditions, the possibility of making a diagnosis early in life not only helps avoid unnecessary diagnostic testing, but is also beneficial to the patient's families because genetic counseling and prenatal diagnosis can be offered. This test includes 32 of 34 core conditions* included in the RUSP and all secondary conditions listed with the RUSP. Our screening approach is designed to identify all newborns affected with at least the classic variants of the diseases, but is not expected to detect milder forms of these conditions (see table). The NBSE / Newborn Screening Expanded Panel, Blood Spot includes the same testing as the this test, but also includes screening for an additional 4 lysosomal storage disorders (Krabbe, Fabry, Gaucher, and Niemann-Pick A/B diseases), guanidinoacetate methyltransferase (GAMT) deficiency, and glucose-6-phosphate dehydrogenase (G6PD) deficiency. *This test does not screen for critical congenital heart disease and congenital hearing loss, both of which are tested in the nursery using methods other than blood spots (audiometry, pulse oximetry). RUSP Core Conditions Abbreviation NBSR NBSE Method Disease States (result field) Propionic acidemia PROP + + MS/MS Organic acid disorders Methylmalonic acidemia due to methylmalonyl-CoA mutase deficiency MUT + + MS/MS Organic acid disorders Methylmalonic acidemia, cbIA type and cbIB type Cbl A,B + + MS/MS Organic acid disorders Isovaleric acidemia IVA + + MS/MS Organic acid disorders 3-Methylcrotonyl-CoA carboxylase 1 and 2 deficiency 3-MCC + + MS/MS Organic acid disorders 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency HMG + + MS/MS Organic acid disorders Holocarboxylase synthetase deficiency MCD + + MS/MS Organic acid disorders Beta-ketothiolase deficiency BetaKT + + MS/MS Organic acid disorders Glutaric acidemia type I GA1 + + MS/MS Organic acid disorders Carnitine deficiency, systemic primary CUD + + MS/MS Organic acid disorders Medium-chain acyl-CoA dehydrogenase deficiency MCAD + + MS/MS Organic acid disorders Very long-chain acyl-CoA dehydrogenase deficiency VLCAD + + MS/MS Fatty acid oxidation disorders Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency LCHAD + + MS/MS Fatty acid oxidation disorders Medium-chain acyl-CoA dehydrogenase deficiency MCAD + + MS/MS Fatty acid oxidation disorders Argininosuccinic acidemia ASA + + MS/MS Amino acid disorders Citrullinemia, type I CIT + + MS/MS Amino acid disorders Maple syrup urine disease MSUD + + MS/MS Amino acid disorders Homocystinuria due to cystathionine beta-synthase deficiency HCY + + MS/MS Amino acid disorders...
<table>
<thead>
<tr>
<th>Condition</th>
<th>Test Method</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylketonuria (PKU)</td>
<td>MS/MS</td>
<td>detection of amino acid disorders such as tyrosinemia, congenital adrenal hyperplasia</td>
</tr>
<tr>
<td>Tyrosinemia, type I (TYR I)</td>
<td>MS/MS</td>
<td>diagnosis of amino acid disorders</td>
</tr>
<tr>
<td>Tyrosinemia, type III (TYR III)</td>
<td>MS/MS</td>
<td>diagnosis of amino acid disorders</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia (CAH)</td>
<td>MS/MS</td>
<td>diagnosis of amino acid disorders</td>
</tr>
<tr>
<td>Sickle cell anemia (Hb S)</td>
<td>Capillary electrophoresis</td>
<td>used for diagnosis of S, S disease</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>Capillary electrophoresis</td>
<td>for diagnosis of S, S disease</td>
</tr>
<tr>
<td>Hemoglobinopathy</td>
<td>Capillary electrophoresis</td>
<td>for diagnosis of S, S disease</td>
</tr>
<tr>
<td>Methylmalonic acidemia (MMA)</td>
<td>MS/MS</td>
<td>diagnosis of organic acid disorders</td>
</tr>
<tr>
<td>Methylmalonic acidemia (MMA)</td>
<td>MS/MS</td>
<td>diagnosis of organic acid disorders</td>
</tr>
<tr>
<td>Methylmalonic acidemia (MMA)</td>
<td>MS/MS</td>
<td>diagnosis of organic acid disorders</td>
</tr>
<tr>
<td>Methylmalonic acidemia (MMA)</td>
<td>MS/MS</td>
<td>diagnosis of organic acid disorders</td>
</tr>
<tr>
<td>Methylmalonic acidemia (MMA)</td>
<td>MS/MS</td>
<td>diagnosis of organic acid disorders</td>
</tr>
</tbody>
</table>

**Useful For:** Presymptomatic identification of Recommended Uniform Screening Panel (RUSP) disorders only to allow for early initiation of treatment and consequent improvement in the long-term prognosis of affected patients.

**Interpretation:** An interpretive report is provided. The quantitative measurements of informative metabolites and related ratios and their bioinformatics evaluation using the Collaborative Laboratory
Integrated Reports (CLIR) system support the initial interpretation of the complete profile and may suggest the need to perform the measurement of more specific biomarkers using the original newborn screen specimen (second-tier test). Nevertheless, abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis, independent biochemical (ie, in vitro enzyme assay) or molecular genetic analyses are required, many of which are offered within Mayo Clinic's Division of Laboratory Genetics and Genomics. The reports are in text form only. In a case with a completely normal profile, where the interpretation is reported as negative for all of the listed groups of conditions, no values are provided. A report for an abnormal screening result includes a quantitative result for the relevant abnormal biomarkers including those of a second-tier test when applicable, the CLIR score indicating the similarity of the newborn’s results to those derived from known patients with the relevant disease, a detailed interpretation of the results, and recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis).

**Reference Values:**

**Clinical References:**

**Newborn Screening Expanded Panel, Blood Spot**

**Clinical Information:** Newborn screening as a public health measure was initiated in the early 1960s for the identification of infants affected with phenylketonuria (PKU). Since then, additional genetic and nongenetic conditions were included in screening programs. The goal of newborn screening is to detect diagnostic markers of selected disorders in blood spots collected from presymptomatic newborns. Early identification of affected newborns allows for early initiation of treatment to avoid mortality, morbidity, and disabilities due to these disorders. The US Secretary of Health and Human Services (HHS) recommends all programs screen for 34 core disorders (www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpanel/). These conditions are considered to fulfill 3 basic principles: -Condition is identifiable at a period of time (12-48 hours after birth) at which it would not ordinarily be clinically detected. -Test with appropriate sensitivity and specificity is available. -Demonstrated benefits of early detection, timely intervention, and efficacious treatment. The 34 core disorders comprise the Recommended Uniform Screening Panel (RUSP). Screening tests do not conclusively determine disease status, but measure analytes, which in most cases are not specific for a particular disease. This is the reason why the HHS Secretary also recognizes more than 25 additional conditions as secondary targets that do not meet all inclusion criteria, but are identified nevertheless because most of them are components of the differential diagnosis of screening results observed in core conditions. Even for the secondary conditions, the possibility of making a diagnosis early in life not only helps avoid unnecessary diagnostic testing, but is also beneficial to the patient's families because genetic counseling and prenatal diagnosis can be offered. This test includes 32 of 34 core conditions* included in the RUSP and all secondary conditions listed with the RUSP. In addition, it is expanded to include screening for an additional 4 lysosomal
storage disorders (Krabbe, Fabry, Gaucher, and Niemann-Pick types A and B diseases),
guanidinoacetate methyltransferase (GAMT) deficiency, and glucose-6-phosphate dehydrogenase
(G6PD) deficiency. Our screening approach is designed to identify all newborns affected with at least
the classic variants of the diseases, but is not expected to detect milder forms of these conditions (see
table). *This test does not screen for critical congenital heart disease and congenital hearing loss, both
of which are tested in the nursery using methods other than blood spots (audiometry, pulse oximetry).
RUSP Core Conditions Abbreviation NBSR NBSE Method Disease States (result field) Propionic
acidemia PROP + + MS/MS Organic acid disorders Methylmalonic acidemia due to
methylmalonyl-CoA mutase deficiency MUT + + MS/MS Organic acid disorders Methylmalonic
acidemia, cblA type and cblB type Cbl A,B + + MS/MS Organic acid disorders Isovaleric acidemia
IVA + + MS/MS Organic acid disorders 3-Methylcrotonyl-CoA carboxylase 1 and 2 deficiency 3-MCC
+ + MS/MS Organic acid disorders 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency HMG + +
MS/MS Organic acid disorders Holocarboxylase synthetase deficiency MCD + + MS/MS Organic acid
disorders Beta-ketothiolase deficiency BetaKT + + MS/MS Organic acid disorders Glutaric acidemia
type I GA1 + + MS/MS Organic acid disorders Carnitine deficiency, systemic primary CUD + +
MS/MS Fatty acid oxidation disorders Medium-chain acyl-CoA dehydrogenase deficiency MCAD + +
MS/MS Fatty acid oxidation disorders Very long-chain acyl-CoA dehydrogenase deficiency VLCAD + +
+ MS/MS Fatty acid oxidation disorders Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
LCHAD + + MS/MS Fatty acid oxidation disorders Mitochondrial trifunctional protein deficiency TFP
+ + MS/MS Fatty acid oxidation disorders Argininosuccinic acidemia ASA + + MS/MS Amino acid
disorders Citrullinemia, type I CITT + + MS/MS Amino acid disorders Maple syrup urine disease MSUD
+ + MS/MS Amino acid disorders Homocystinuria due to cystathionine beta-synthase deficiency HCY
+ + MS/MS Amino acid disorders Phenylketonuria PKU + + MS/MS Amino acid disorders
Tyrosinemia, type I TYR I + + MS/MS Amino acid disorders Primary congenital hyperthyroidism CH + +
Immunooassay Congenital hyperplasia CAH + + Immunooassay Congenital adrenal hyperplasia S.S disease (Sickle cell anemia) Hb Sss + + Capillary electrophoresis
Hemoglobinopathies S, Beta-thalassemia Hb S/betaTh + + Capillary electrophoresis
Hemoglobinopathies S,C disease Hb S/C + + Capillary electrophoresis Hemoglobinopathies Biotinidase
deficiency BIOT + + Colorimetric assay Biotinidase deficiency Cystic fibrosis CF + + Immunooassay
Cystic fibrosis Classic galactosemia GALT + + Colorimetric assay Galactosemia Severe combined
immunodeficiencies SCID + + ddPCR Severe combined immune deficiency Mucopolysaccharidosis
type I MPS I + + MS/MS Lysosomal storage disorders Glycogen storage disease type II (Pompe
disease) GSD II + + MS/MS Lysosomal storage disorders Adrenoleukodystrophy X-ALD + + MS/MS
X-linked adrenoleukodystrophy RUSP Secondary Conditions Methylmalonic acidemia and
homocystinemia (Cbl C, D) Cbl C,D + + MS/MS Organic acid disorders Malonyl-CoA decarboxylase
deficiency MAL + + MS/MS Organic acid disorders Isobutyryl-CoA dehydrogenase deficiency IBG + +
MS/MS Organic acid disorders 2-Methylbutryl-CoA dehydrogenase deficiency 2MBG + + MS/MS
Organic acid disorders 2-Methyl-3-hydroxybutyric aciduria 2MBG + + MS/MS Organic acid
disorders 3-Methylglutaconic acidemia 3MGA + + MS/MS Organic acid disorders
Acyl-CoA dehydrogenase deficiency SCAD + + MS/MS Organic acid disorders
Acyl-CoA dehydrogenase deficiency IVA + + MS/MS Fatty acid oxidation disorders
Medium/short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency M/SCHAD + + MS/MS Fatty acid
oxidation disorders Glutaric acidemia type II (Multiple acyl-CoA dehydrogenase deficiency) GA2 + +
MS/MS Fatty acid oxidation disorders Medium-chain 3-ketoacyl-CoA thioloase deficiency MCAT + +
MS/MS Fatty acid oxidation disorders 2,4-Dienoyl-CoA reductase deficiency DE RED + + MS/MS
Fatty acid oxidation disorders Carnitine palmitoyltransferase type I deficiency CPT IA + + MS/MS
Fatty acid oxidation disorders Carnitine palmitoyltransferase type II deficiency CPT II + + MS/MS
Fatty acid oxidation disorders Carnitine-acylcarnitine translocase deficiency CACT + + MS/MS Fatty
acid oxidation disorders Arginemia ARG + + MS/MS Amino acid disorders Citrullinemia, type II CITT
+ + MS/MS Amino acid disorders Hypermethioninemia MET + + MS/MS Amino acid disorders
Benign hyperphenylalaninemia H-PHE + + MS/MS Amino acid disorders Bioperin defect in cofactor
biosynthesis or regeneration BIOPT (BS/REG) + + MS/MS Amino acid disorders Tyrosinemia, type II
TYR II + + MS/MS Amino acid disorders Tyrosinemia, type III TYR III + + MS/MS Amino acid
disorders Various other hemoglobinopathies Var Hb + + Capillary electrophoresis Hemoglobinopathies
Galactose epimerase deficiency GALE + + Colorimetric assay Galactosemia Galactokinase deficiency
GALK + + Colorimetric assay Galactosemia T-cell related lymphocyte deficiencies SCID + + ddPCR
Severe combined immune deficiency Peroxisomal acyl-CoA oxidase deficiency Acyl-CoA oxidase
MS/MS X-linked adrenoleukodystrophy D-bifunctional protein deficiency BFP + + MS/MS X-linked
adrenoleukodystrophy Peroxisome biogenesis disorders (Zellweger spectrum disorders) PBD + +
MS/MS X-linked adrenoleukodystrophy Other conditions included or considered by individual states/countries Methylmalonic acidemia and homocystinuria, cbl D type Cbl D-var1 + + MS/MS Organic acid disorders Homocystinuria-Megaloblastic anemia, cbl E type Cbl E + + MS/MS Organic acid disorders Homocystinuria-Megaloblastic anemia, cbl G type Cbl G + + MS/MS Organic acid disorders Homocystinuria due to MTHFR deficiency MTHFR + + MS/MS Amino acid disorders Glucose-6-phosphate dehydrogenase (G6PD) deficiency G6PD - + Fluorometric G6PD deficiency Fabry disease Fabry - + MS/MS Lysosomal storage disorders Gaucher disease Gaucher - + MS/MS Lysosomal storage disorders Niemann-Pick Disease, type A and type B NPA/B - + MS/MS Lysosomal storage disorders Krabbe disease Krabbe - + MS/MS Lysosomal storage disorders Guanidinoacetate Methyltransferase (GAMT) deficiency GAMT** - + MS/MS Disorders of creatine metabolism **Other creatine deficiency disorders may be detected. NBSE=Newborn Screening Expanded Panel, Blood Spot NBSR=Newborn Screen Recommended Panel, Blood Spot MS/MS=Tandem Mass Spectrometry ddPCR=Digital Droplet Polymerase Chain Reaction MTHFR=Methylenetetrahydrofolate Reductase Enzyme Recommendations for testing to follow up on abnormal NBSE results can be found at www.acmg.net - ACT Sheets. For lysosomal storage diseases, GAMT deficiency, G6PD deficiency, and XALD ACT sheets, see Special Instructions.

Useful For: Presymptomatic identification of disorders for which we can screen using an expanded panel to allow for early initiation of treatment and consequent improvement in the long-term prognosis of affected patients

Interpretation: An interpretive report is provided. The quantitative measurements of informative metabolites and related ratios and their bioinformatic evaluation using the Collaborative Laboratory Integrated Reports (CLIR) system support the initial interpretation of the complete profile and may suggest the need to perform the measurement of more specific biomarkers using the original newborn screen specimen (second-tier test). Nevertheless, abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis, independent biochemical (ie, in vitro enzyme assay) or molecular genetic analyses are required, many of which are offered within Mayo Clinic's Division of Laboratory Genetics and Genomics. The reports are in text form only. In a case with a completely normal profile, where the interpretation is reported as negative for all of the listed groups of conditions, no values are provided. A report for an abnormal screening result includes a quantitative result for the relevant abnormal biomarkers including those of a second-tier test when applicable, the CLIR score indicating the similarity of the newborn's results to those derived from known patients with the relevant disease, a detailed interpretation of the results, and recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis).

Reference Values:
Negative

Next-Generation Sequencing (NGS) Multiple Myeloma
Pre-Analysis Cell Sorting, Bone Marrow

Clinical Information: Testing allows for further risk categorization of the disease through the identification of additional abnormalities of prognostic and potentially therapeutic value. Application of targeted NGS-based analysis is a useful adjunct to the standard evaluation of MM patients at diagnosis and relapse.

Useful For: Evaluation of multiple myeloma at the time of diagnosis, for prognostic and potential therapeutic indications
Determine the presence of new clinically important gene mutation changes at relapse

Interpretation: An interpretive report is provided.

Reference Values:
Only orderable as a reflex. See NGSMM / NGSM Multiple Myeloma

Next-Generation Sequencing (NGS), Acute Myeloid Leukemia

Clinical Information: Next-generation sequencing (NGS) is a rapidly evolving and complex methodology that can interrogate multiple regions of genomic tumor DNA in a single assay. Many hematologic neoplasms, including acute myeloid leukemia (AML), are characterized by morphologic or phenotypic similarities, but can have characteristic somatic mutations in many genes. In addition, many cases of AML lack a clonal cytogenetic finding at diagnosis (normal karyotype) and can be better classified according to gene mutation profile. The presence and pattern of gene mutations in AML can provide critical prognostic information and may help in guiding therapeutic management decisions by physicians.

Useful For: Evaluation of acute myeloid leukemia (AML) at the time of diagnosis, to assist in appropriate classification and prognosis using a 19-gene panel
Evaluation to determine if a different gene mutation profile is present at the time of AML relapse

Interpretation: Mutations (gene alterations) identified, if present. An interpretive report will be provided.

Reference Values:
An interpretive report will be provided.


Next-Generation Sequencing (NGS), Acute Myeloid Leukemia, 8-Gene Panel

Clinical Information: Next-generation sequencing (NGS) is a rapidly evolving and complex methodology that can interrogate multiple regions of genomic tumor DNA in a single assay. Many hematologic neoplasms, including acute myeloid leukemia (AML), are characterized by morphologic or phenotypic similarities, but can have characteristic somatic mutations in many genes. In addition, many cases of AML lack a clonal cytogenetic finding at diagnosis (normal karyotype) and can be better classified according to gene mutation profile. The presence and pattern of gene mutations in AML can
provide critical prognostic information and may help in guiding therapeutic management decisions by physicians.

**Useful For:** Evaluation of acute myeloid leukemia (AML) at the time of diagnosis, to assist in appropriate classification and prognosis, using an 8-gene panel. Evaluation to determine if a different gene mutation profile is present at the time of AML relapse.

**Interpretation:** Mutations (gene alterations) identified, if present. An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**NGSMM Next-Generation Sequencing (NGS), Multiple Myeloma**

**Clinical Information:** Multiple myeloma (MM) is a malignancy of bone marrow plasma cells with an annual incidence of 200,000 per annum. Comprehensive clinical, radiologic and laboratory evaluation can initially stratify patients by disease phase and burden. Cytogenetic and FISH studies are important to help classify MM into standard, intermediate, and high risk groups. Advances in nontargeted therapies (including autologous bone marrow transplantation) have significantly improved the outcome of many patients; however, most patients with myeloma suffer relapse after initial treatment. Clinical next-generation sequencing (NGS) technology has enabled a deeper and more detailed evaluation of MM genetics. Testing allows for further risk categorization of the disease through the identification of additional abnormalities of prognostic and potentially therapeutic value. Application of targeted NGS-based analysis is a useful adjunct to the standard evaluation of MM patients at diagnosis and relapse. This test comprises a DNA-based multigene panel (NGSMM) that includes preanalytic plasma cell enrichment, NGS (Illumina platform), and detailed analysis resulted in a clinical report.

**Useful For:** Evaluation of multiple myeloma at the time of diagnosis, for prognostic and potential therapeutic indications. Identification of the presence of new, clinically important, gene mutation changes at relapse.

**Interpretation:** An interpretive report will be provided that includes the mutations (gene alterations) identified, if present.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Nickel, 24 Hour, Urine

Clinical Information: Nickel (Ni) is a silvery white metal that is widely distributed in the earth's crust. Nickel is essential for the catalytic activity of some plant and bacterial enzymes but its role in humans has not been defined. Elemental Ni may be essential for life at very low concentrations and is virtually nontoxic. Nickel is commonly used in industry. It is a pigment in glass, ceramics, and fabric dyes; is converted in the Mond process to nickel carbonyl, Ni(CO)4, and used as a catalyst in petroleum refining and in the plastics industry, is frequently employed in the production of metal alloys (which are popular for their anticorrosive and hardness properties) in nickel-cadmium rechargeable batteries, and is used as a catalyst in hydrogenation of oils. Ni(CO)4, a liquid with low vapor pressure, is one of the most toxic chemicals known to man. Ni(CO)4 is absorbed after inhalation, readily crosses all biological membranes, and noncompetitively inhibits ATP-ase and RNA polymerase. Breathing the vapors of Ni(CO)4 binds avidly to hemoglobin with resultant inability to take up oxygen. The affinity for hemoglobin is higher than carbon monoxide. The binding to hemoglobin is the main transport mechanism for spreading Ni(CO)4 throughout the body. Urine is the specimen of choice for the determination of Ni exposure via inhalation. Patients undergoing dialysis are exposed to Ni and accumulate Ni in blood and other organs; there appears to be no adverse health effects from this exposure. Hypernickelemia has been observed in patients undergoing renal dialysis. At the present time, this is considered to be an incidental finding as no correlation with toxic events has been identified. Routine monitoring of patients undergoing dialysis is currently not recommended. Breathing dust high in Ni content has been associated with development of neoplasms of the respiratory system and nasal sinuses. Most reactions to Ni are localized skin sensitivity and allergic skin disorders that occur on contact with nickel-containing alloys. These reactions do not correlate to blood concentrations; patients experiencing skin sensitivity reactions to nickel are likely to have normal circulating concentrations of Ni.

Useful For: Detecting nickel toxicity in patients exposed to nickel carbonyl

Interpretation: Values of 3.6 mcg/24-hour specimen and higher represent possible environmental or occupational exposure. Nickel (Ni) concentrations above 50 mcg/24-hour specimen are of concern, suggesting excessive exposure. Clinical concern about Ni toxicity should be limited to patients with potential for exposure to toxic Ni compounds such as nickel carbonyl. Hypernickelemia, in the absence of exposure to that specific form of Ni, may be an incidental finding or could be due to specimen contamination.

Reference Values:
- 0-17 years: not established
- > or =18 years: <3.6 mcg/24h

Clinical References:

Nickel, Serum

Clinical Information: Nickel (Ni) is a silvery white metal that is widely distributed in the earth's crust. Nickel is essential for the catalytic activity of some plant and bacterial enzymes but its role in humans has not been defined. Elemental nickel may be essential for life at very low concentrations and is virtually nontoxic. Nickel is commonly used in industry. It is a pigment in glass, ceramics, and fabric dyes; is converted in the Mond process to nickel carbonyl, Ni(CO)4, and used as a catalyst in petroleum refining and in the plastics industry, is frequently employed in the production of metal alloys (which are popular for their anticorrosive and hardness properties) in nickel-cadmium rechargeable batteries, and is used as a catalyst in hydrogenation of oils. Ni(CO)4, a liquid with low vapor pressure, is one of the most toxic chemicals known to man. Ni(CO)4 is absorbed after inhalation, readily crosses all biological membranes, and noncompetitively inhibits ATP-ase and RNA polymerase. When Ni(CO)4 vapor is inhaled it binds avidly to hemoglobin with resultant inability to take up oxygen. The affinity for hemoglobin is higher than carbon monoxide. The binding to hemoglobin is the main transport mechanism for spreading Ni(CO)4 throughout the body. Urine is the specimen of choice for the determination of Ni exposure via inhalation. Patients undergoing dialysis are exposed to Ni and accumulate Ni in blood and other organs; there appears to be no adverse health effects from this exposure. Hypernickelemia has been observed in patients undergoing renal dialysis. At the present time, this is considered to be an incidental finding as no correlation with toxic events has been identified. Routine monitoring of patients undergoing dialysis is currently not recommended. Breathing dust high in Ni content has been associated with development of neoplasms of the respiratory system and nasal sinuses. Most reactions to Ni are localized skin sensitivity and allergic skin disorders that occur on contact with nickel-containing alloys. These reactions do not correlate to blood concentrations; patients experiencing skin sensitivity reactions to nickel are likely to have normal circulating concentrations of Ni.

Useful For: Detecting nickel toxicity in patients exposed to nickel carbonyl

Interpretation: Values of 3.6 mcg/24-hour specimen and higher represent possible environmental or occupational exposure. Nickel (Ni) concentrations above 50 mcg/24-hour specimen are of concern, suggesting excessive exposure. Clinical concern about Ni toxicity should be limited to patients with potential for exposure to toxic Ni compounds such as nickel carbonyl. Hypernickelemia, in the absence of exposure to that specific form of Ni, may be an incidental finding or could be due to specimen contamination.

Reference Values:
- 0-17 years: not established
- > or =18 years: <3.6 mcg/24h

Clinical References:
for spreading Ni(CO)4 throughout the body. Urine is the specimen of choice for the determination of nickel exposure via inhalation. Patients undergoing dialysis are exposed to nickel and accumulate nickel in blood and other organs; there appear to be no adverse health affects from this exposure. Hypernickelemia has been observed in patients undergoing renal dialysis. At the present time, this is considered to be an incidental finding as no correlation with toxic events has been identified. Routine monitoring of patients undergoing dialysis is currently not recommended. Breathing dust high in nickel content has been associated with development of neoplasms of the respiratory system and nasal sinuses. Most reactions to nickel are localized skin sensitivity and allergic skin disorders that occur on contact with nickel-containing alloys. These reactions do not correlate to blood concentrations; patients experiencing skin sensitivity reactions to nickel are likely to have normal circulating concentrations of nickel.

**Useful For:** Urine nickel is the test of choice for detecting nickel toxicity in patients exposed to nickel carbonyl

**Interpretation:** Values >2.0 ng/mL represent possible environmental or job-related exposure. Toxic concentrations are > or =10 ng/mL. Normal values are based on a Mayo Clinic study using healthy volunteers. Toxic values have been deduced from observation and unpublished internal study. Clinical concern about nickel toxicity should be limited to patients with potential for exposure to toxic nickel compounds such as nickel carbonyl. Hypernickelemia, in the absence of exposure to that specific form of nickel, may be an incidental finding or could be due to specimen contamination.

**Reference Values:**

<2.0 ng/mL


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**Nickel/Creatinine Ratio, Random, Urine**

**Clinical Information:** Nickel (Ni), a silvery white metal widely distributed in the earth's crust, is essential for the catalytic activity of some plant and bacterial enzymes but its role in humans has not been defined. Elemental Ni may be essential for life at very low concentrations and is virtually nontoxic. Nickel is commonly used in industry. It is a pigment in glass, ceramics and fabric dyes. It is converted in the Mond process to nickel carbonyl, NiCO(4), and used as a catalyst in petroleum refining and in the plastics industry, is frequently employed in the production of metal alloys (which are popular for their anticorrosive and hardness properties) in Ni-cadmium rechargeable batteries, and is used as a catalyst in hydrogenation of oils. NiCO(4) is very toxic. NiCO(4), a liquid with low vapor pressure, is one of the most toxic chemicals known to man. NiCO(4) is absorbed after inhalation, readily crosses all biological membranes, and noncompetitively inhibits ATP-ase and RNA polymerase. NiCO(4) binds avidly to hemoglobin with resultant inability to take up oxygen. The affinity for hemoglobin is higher than carbon monoxide. The binding to hemoglobin is the main transport mechanism for spreading NiCO(4) throughout the body. Urine is the specimen of choice for the determination of Ni exposure via inhalation. Patients undergoing dialysis are exposed to Ni and accumulate Ni in blood and other organs; there appear to be no adverse health effects from this exposure. Hypernickelemia has been observed in patients undergoing renal dialysis. At the present time, this is considered to be an incidental finding as no correlation with toxic events has been identified. Routine monitoring of patients undergoing dialysis is currently not recommended. Breathing dust high in Ni content has been associated with development of neoplasms of the respiratory system and nasal sinuses. Most reactions to Ni are localized skin sensitivity and allergic skin disorders that occur on contact with Ni-containing alloys. These reactions do not correlate to urine concentrations; patients experiencing skin sensitivity reactions to Ni are likely to have normal Ni excretion.

**Useful For:** Urine nickel is the test of choice for detecting nickel toxicity in patients exposed to nickel carbonyl.
**Interpretation:** Values of 3.8 mcg/g creatinine and higher for males, or 4.3 mcg/g creatinine and higher for females, represent possible environmental or occupational exposure. Nickel (Ni) concentrations above 50 mcg/g creatinine are of concern, suggesting excessive exposure. Clinical concern about Ni toxicity should be limited to patients with potential for exposure to toxic Ni compounds such as nickel carbonyl. Hypernickelemia, in the absence of exposure to that specific form of Ni, may be an incidental finding or could be due to specimen contamination.

**Reference Values:**

0-17 years: not established  
Males > or =18 years: <3.8 mcg/g creatinine  
Females > or =18 years: <4.3 mcg/g creatinine

**Clinical References:**  

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**Nicotine and Metabolites, Serum**

**Clinical Information:** Fatalities related to tobacco use are a leading cause of death in United States. Nicotine, coadministered in tobacco products such as cigarettes, pipe tobacco, cigars, or chew, is an addicting substance that causes individuals to continue use of tobacco despite concerted efforts to quit. Nicotine stimulates dopamine release and increases dopamine concentration in the nucleus accumbens, a mechanism that is thought to be the basis for addiction for drugs of abuse. Nicotine-dependent patients use tobacco products to achieve a peak serum nicotine value of 30 to 50 ng/mL, the concentration at which the nicotine high is maximized. Nicotine is metabolized in the liver to cotinine. Cotinine accumulates in serum in proportion to dose and hepatic metabolism (which is genetically determined); most tobacco users accumulate cotinine in the range of 200 to 800 ng/mL. Serum concentrations of nicotine and metabolites in these ranges indicate the patient is using tobacco or is receiving high-dose nicotine patch therapy. Nicotine is rapidly metabolized, exhibiting an elimination half-life of approximately 2 hours. Cotinine exhibits an apparent elimination half-life of approximately 24 hours. Heavy tobacco users who abstain from tobacco for 2 weeks exhibit serum nicotine values <3.0 ng/mL and cotinine <3.0 ng/mL. Passive exposure to tobacco smoke can cause accumulation of nicotine metabolites in nontobacco users. Serum cotinine has been observed to accumulate up to 8 ng/mL from passive exposure. Tobacco users engaged in programs to abstain from tobacco require support in the form of counseling, pharmacotherapy, and continuous encouragement. Occasionally, counselors may elect to monitor abstinence by biochemical measurement of nicotine and metabolites in serum to verify abstinence. If results of biologic testing indicate the patient is actively using a tobacco product during therapy, additional counseling or intervention may be appropriate.

**Useful For:** Monitoring tobacco use

**Interpretation:** Serum nicotine concentration in the range of 30 to 50 ng/mL with cotinine in the range of 200 to 800 ng/mL indicates the subject is either actively using a tobacco product or on nicotine replacement therapy. To discriminate if a patient on nicotine replacement therapy is also actively using a tobacco product, see NICOU / Nicotine and Metabolites, Urine analysis; the presence of anabasine in urine, a tobacco alkaloid not present in nicotine replacement products, indicates recent tobacco use. Typical findings are as follows: While using a tobacco product:  
- Peak nicotine concentration: 30 to 50 ng/mL  
- Peak cotinine concentration: 200 to 800 ng/mL  
*Higher values may be seen in subjects with high cytochrome P450 2D6 activity Tobacco user after 2 weeks complete abstinence:  
- Nicotine concentration: <3.0 ng/mL  
- Cotinine concentration: <3.0 ng/mL  
Nontobacco user with passive exposure:  
- Nicotine concentration: <3.0 ng/mL  
- Cotinine concentration: <8.0 ng/mL  
Nontobacco user with no passive exposure:  
- Nicotine concentration: <3.0 ng/mL  
- Cotinine concentration: <3.0 ng/mL

**Reference Values:**

NICOTINE

Nicotine and Metabolites, Urine

Clinical Information: Tobacco use is the leading cause of death in the United States. Nicotine, coadministered in tobacco products such as cigarettes, pipe, cigar, or chew, is an addicting substance that causes individuals to continue use of tobacco despite concerted efforts to quit. Nicotine stimulates dopamine release and increases dopamine concentration in the nucleus accumbens, a mechanism that is thought to be the basis for addiction for drugs of abuse. Nicotine is rapidly metabolized in the liver to cotinine, exhibiting an elimination half-life of 2 hours. Cotinine exhibits an apparent elimination half-life of 15 hours. Patients using tobacco products excrete nicotine in urine in the concentration range of 1,000 to 5,000 ng/mL. Cotinine accumulates in urine in proportion to dose and hepatic metabolism (which is genetically determined); most tobacco users excrete cotinine in the range of 1,000 to 8,000 ng/mL. Urine concentrations of nicotine and metabolites in these ranges indicate the subject is using tobacco or is receiving high-dose nicotine patch therapy. In addition to nicotine and metabolites, tobacco products also contain other alkaloids that can serve as unique markers of tobacco use. Two such markers are anabasine and nornicotine. Anabasine is present in tobacco products, but not nicotine replacement therapies. Nornicotine is present as an alkaloid in tobacco products and as a metabolite of nicotine. The presence of anabasine greater then 10 ng/mL or nornicotine greater then 30 ng/mL in urine indicates current tobacco use, irrespective of whether the subject is on nicotine replacement therapy. The presence of nornicotine without anabasine is consistent with use of nicotine replacement products. Heavy tobacco users who abstain from tobacco for 2 weeks exhibit urine nicotine values below 30 ng/mL, cotinine values below 50 ng/mL, anabasine levels below 2 ng/mL, and nornicotine levels below 2 ng/mL. Passive exposure to tobacco smoke can cause accumulation of nicotine metabolites in nontobacco users. Urine cotinine has been observed to accumulate up to 20 ng/mL from passive exposure. Neither anabasine nor nornicotine accumulates from passive exposure. Tobacco users engaged in programs to abstain from tobacco require support in the form of counseling, pharmacotherapy, and continuous encouragement. Occasionally, counselors may elect to monitor abstinence by biochemical measurement of nicotine and metabolites in a random urine specimen to verify abstinence. If results of biologic testing indicate the patient is actively using a tobacco product during therapy, additional counseling or intervention may be appropriate. Quantification of urine nicotine and metabolites while a patient is actively using a tobacco product is useful to define the concentrations that a patient achieves through self-administration of tobacco. Nicotine replacement dose can then be tailored to achieve the same concentrations early in treatment to assure adequate nicotine replacement so the patient may avoid the strong craving they may experience early in the withdrawal phase. This can be confirmed by measurement of urine nicotine and metabolite concentrations at steady-state (2-3 days after replacement therapy is started). Once the patient is stabilized on the dose necessary to achieve complete replacement and responding well to therapy, the replacement dose can be slowly tapered to achieve complete withdrawal.

Useful For: Monitoring tobacco use Monitoring patients on nicotine-replacement therapy for concurrent use of tobacco products

Interpretation: Urine nicotine in the range of 1,000 to 5,000 ng/mL with cotinine in the range of 1,000 to 8,000 ng/mL indicates the subject is either actively using a tobacco product or on high-dose nicotine patch therapy. The presence of anabasine and nornicotine indicates a subject on patch therapy who is actively using a tobacco product. Typical findings are as follows: While using a tobacco product:
- Peak nicotine concentration: 1,000 to 5,000 ng/mL
- Peak cotinine concentration: 1,000 to 8,000 ng/mL
- Anabasine concentration: 10 to 500 ng/mL
- Nornicotine concentration: 30 to 900 ng/mL

Tobacco user after 2 weeks complete abstinence:
- Nicotine concentration: <30 ng/mL
- Cotinine concentration: <50 ng/mL
- Anabasine concentration: <2.0 ng/mL
- Nornicotine concentration: <2.0 ng/mL

Nontobacco user with passive exposure:
- Nicotine concentration: <20 ng/mL
- Cotinine concentration: <20 ng/mL
- Anabasine concentration: <2.0 ng/mL
- Nornicotine concentration: <2.0 ng/mL

Nontobacco user with no passive exposure:
- Nicotine concentration: <5.0 ng/mL
- Cotinine concentration: <5.0 ng/mL
- Anabasine concentration: <2.0 ng/mL
- Nornicotine concentration: <2.0 ng/mL

Reference Values:
Non-tobacco user with no passive exposure:
- NICOTINE
  <5.0 ng/mL
- COTININE
  <5.0 ng/mL
- ANABASINE
  <2.0 ng/mL
- NORNICOTINE
  <2.0 ng/mL

Clinical References:

**Clinical Information:** Fatalities related to tobacco use are a leading cause of death in United States. Nicotine, coadministered in tobacco products such as cigarettes, pipe tobacco, cigars, or chew, is an addicting substance that causes individuals to continue use of tobacco despite concerted efforts to quit. Nicotine stimulates dopamine release and increases dopamine concentration in the nucleus accumbens, a mechanism that is thought to be the basis for addiction for drugs of abuse. Nicotine-dependent patients use tobacco products to achieve a peak serum nicotine value of 30 to 50 ng/mL, the concentration at which the nicotine high is maximized. Nicotine is metabolized in the liver to cotinine. Cotinine accumulates in serum in proportion to dose and hepatic metabolism (which is genetically determined); most tobacco users accumulate cotinine in the range of 200 to 800 ng/mL. Serum concentrations of nicotine and metabolites in these ranges indicate the patient is using tobacco or is receiving high-dose nicotine patch therapy. Nicotine is rapidly metabolized, exhibiting an elimination half-life of approximately 2 hours. Cotinine exhibits an apparent elimination half-life of approximately 24 hours. Heavy tobacco users who abstain from tobacco for 2 weeks exhibit serum nicotine values less than 3.0 ng/mL and cotinine less than 3.0 ng/mL. Passive exposure to tobacco smoke can cause accumulation of nicotine metabolites in nontobacco users. Serum cotinine has been observed to accumulate up to 8 ng/mL from passive exposure. Tobacco users engaged in programs to abstain from tobacco require support in the form of counseling, pharmacotherapy, and continuous encouragement. Occasionally, counselors may elect to monitor abstinence by biochemical measurement of nicotine and metabolites in serum to verify abstinence. If results of biologic testing indicate the patient is actively using a tobacco product during therapy, additional counseling or intervention may be appropriate.

**Useful For:** Monitoring tobacco use

**Interpretation:** Serum nicotine concentration in the range of 30 to 50 ng/mL with cotinine in the range of 200 to 800 ng/mL indicates the subject is either actively using a tobacco product or on nicotine replacement therapy. To discriminate if a patient on nicotine replacement therapy is also actively using tobacco products, see NICOU / Nicotine and Metabolites, Urine analysis; the presence of anabasine in urine, a tobacco alkaloid not present in nicotine replacement products, indicates recent tobacco use.
Typical findings are as follows: While using a tobacco product:
- Peak nicotine concentration: 30 to 50 ng/mL
- Peak cotinine concentration: 200 to 800 ng/mL
* Higher values may be seen in subjects with high cytochrome P450 2D6 activity
Tobacco user after 2 weeks complete abstinence:
- Nicotine concentration: <3.0 ng/mL
- Cotinine concentration: <3.0 ng/mL
Nontobacco user with passive exposure:
- Nicotine concentration: <3.0 ng/mL
- Cotinine concentration: <8.0 ng/mL
Nontobacco user with no passive exposure:
- Nicotine concentration: <3.0 ng/mL
- Cotinine concentration: <3.0 ng/mL

**Reference Values:**

NICOTINE
<3.0 ng/mL

COTININE
<3.0 ng/mL

**Clinical References:**

**Niemann-Pick Disease, Types A and B, Full Gene Analysis**

**Clinical Information:** Niemann-Pick disease (types A and B) is an autosomal recessive lysosomal storage disease caused by a deficiency of the enzyme acid sphingomyelinase. The clinical presentation of type A disease is characterized by jaundice, progressive loss of motor skills, feeding difficulties, learning disabilities, and hepatosplenomegaly. Death usually occurs by age 3. Type B disease is generally milder, though variable in its clinical presentation. Most type B patients do not have neurologic involvement and survive to adulthood. Mutations in the SMPD1 gene are responsible for the clinical manifestations of Niemann-Pick disease types A and B. Although this disease is panethnic, it has a significantly higher frequency in individuals of Ashkenazi Jewish and Northern African descent. The carrier rate for type A in the Ashkenazi Jewish population is 1/90. There are 3 common mutations in the Ashkenazi Jewish population: L302P, R496L, and sP330, which account for approximately 97% of mutant alleles in this population. The deltaR608 mutation accounts for approximately 90% of the type B mutant alleles in individuals from the Maghreb region of North Africa and 100% of the mutant alleles in Gran Canaria Island. Targeted mutation analysis (NPABP / Niemann-Pick Disease, Types A and B, Mutation Analysis) for these 4 mutations is thought to detect 90% of the mutant alleles leading to acid sphingomyelinase deficiency. Full gene analysis of the SMPD1 gene should be utilized to detect private mutations in individuals with abnormal enzyme activity and 1 or no mutations detected by the panel of common mutations. NPABP / Niemann-Pick Disease, Types A and B, Mutation Analysis is also the recommended test for carrier screening. For diagnostic testing, PLSD / Lysosomal and Peroxisomal Storage Disorders Screen, Blood Spot and OXYBS / Oxyysterols, Blood Spots or OXNP / Oxyysterols, Plasma, should be performed prior to targeted mutation analysis or full gene analysis.

**Useful For:** Confirmation of a diagnosis of Niemann-Pick disease type A or B Carrier screening in cases where there is a family history of Niemann-Pick disease type A or B, but disease-causing mutations have not been identified in an affected individual

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
2. Schuchman EH: The pathogenesis and treatment of acid

**NPABP**

**Niemann-Pick Disease, Types A and B, Mutation Analysis**

**Clinical Information:** Niemann-Pick disease (types A and B) is a lysosomal storage disease caused by a deficiency of the enzyme acid sphingomyelinase. The clinical presentation of type A disease is characterized by jaundice, progressive loss of motor skills, feeding difficulties, learning disabilities, and hepatosplenomegaly. Death usually occurs by age 3. Type B disease is milder, though variable in its clinical presentation. Most type B patients do not have neurologic involvement and survive to adulthood. Mutations in the SMPD1 gene are known to cause Niemann-Pick disease types A and B. The carrier rate for Niemann-pick type A in the Ashkenazi Jewish population is 1 in 90. There are 3 common mutations in the Ashkenazi Jewish population: L302P, R496L, and fsP330. The carrier detection rate for Niemann-Pick type A with these 3 mutations using this assay is approximately 97%. The deltaR608 mutation accounts for approximately 90% of the type B mutant alleles in individuals from the Maghreb region of North Africa and 100% of the mutation alleles in Gran Canaria Island.

**Useful For:** Carrier testing of Niemann-Pick disease types A and B for individuals of Ashkenazi Jewish ancestry
Prenatal diagnosis of Niemann-Pick disease types A and B for at-risk pregnancies
Confirmation of suspected clinical diagnosis of Niemann-Pick disease types A and B in individuals of Ashkenazi Jewish ancestry

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**NIEM**

**Niemann-Pick Type C Detection, Fibroblasts**

**Clinical Information:** Niemann-Pick disease type C (NPC)(1) is caused by a defect in cellular cholesterol trafficking that results in the progressive accumulation of unesterified cholesterol in late endosomes/lysosomes. NPC is considered a lipid storage disorder with variable age of onset (range: perinatal period to adulthood), and highly variable clinical presentation. Most individuals are diagnosed during childhood with symptoms that include ataxia, vertical supranuclear gaze palsy, dystonia, progressive speech deterioration, and seizures. Infants may present with or without hepatosplenomegaly and respiratory failure. Those without liver and pulmonary disease may present with hypotonia and developmental delay. Adult-onset NPC is associated with a slower progression and is characterized by psychiatric illness, ataxia, dystonia, and speech difficulties. The diagnosis of NPC has traditionally relied on the demonstration of impaired cholesterol esterification and positive filipin staining in cultured fibroblasts. Since it has been shown that individuals with NPC also exhibit elevated levels of oxysterol cholestane-3 beta,5 alpha,6 beta-triol (COT), oxysterol testing in plasma (see OXNP / Oxysterols, Plasma) or dried blood spot (see OXYBS / Oxysterols, Blood Spots) is an effective, quick, and less invasive first-tier alternative to cholesterol esterification and filipin staining. The incidence of NPC is approximately 1 in 120,000 to 150,000 live births. NPC is an autosomal recessive condition and is caused by mutations in either the NPC1 or NPC2 genes. About 95% of individuals with NPC have mutations in the NPC1 gene. Mutations may also be identified in the NPC2 gene; see NPCZ / Niemann-Pick Type C Disease, Full Gene Analysis.

**Useful For:** Diagnosis of Niemann-Pick disease type C
Interpretation: Values expected in Niemann-Pick disease type C are below 10% of that found in normal cultured fibroblasts. Values between 10% and 80% of normal will have to be judged on other diagnostic criteria. All values will be followed up by filipin staining for cholesterol.

Reference Values:
If the results indicate that the patient's cultured fibroblasts esterify cholesterol at a level that is <10% of normal cultured fibroblasts and when filipin staining shows excessive storage of free cholesterol, it will be stated that the patient is positive for Niemann-Pick type C disease. All samples will be stained by filipin to see if a milder biochemical phenotype is the likely cause of the Niemann-Pick disease-like clinical picture.

Clinical References:

Niemann-Pick Type C Disease, Full Gene Analysis

Clinical Information: Niemann-Pick type C (NPC) is an inherited disorder of cholesterol transport that results in an accumulation of unesterified cholesterol and lipids in the lysosomal/endosomal system and in various tissues. Although NPC belongs to a group of lysosomal disorders including Niemann-Pick types A and B, these diseases are metabolically and genetically distinct. Niemann-Pick types A and B are caused by mutations in the SMPD1 gene, which encodes the enzyme sphingomyelinase, whereas NPC is caused by mutations in the NPC1 or NPC2 genes. The incidence of NPC is approximately 1 in 120,000 to 1 in 150,000 live births. Age of onset is variable and ranges from the perinatal period to adulthood. Clinical presentation is also highly variable. Infants may present with or without liver disease (hepatosplenomegaly) and respiratory failure. Those without liver and pulmonary disease may present with hypotonia and developmental delay. Most individuals are diagnosed during childhood with symptoms including ataxia, vertical supranuclear gaze palsy, dystonia, progressive speech deterioration, and seizures resulting in death by the second or third decade of life. Adult-onset NPC is associated with a slower progression and is characterized by neurologic and psychiatric problems. NPC is inherited in an autosomal recessive manner, in which affected individuals carry 2 mutations in either the NPC1 or NPC2 gene. Most mutations are family specific, although there are 2 mutations in the NPC1 gene that are more common than others. The G992W mutation is common in the French Acadian population of Nova Scotia. The I1061T mutation is the most common mutation worldwide, and is seen in patients of Hispanic and Western European (United Kingdom and France) descent. Full gene sequencing and analysis for large deletions and duplications of the NPC1 and NPC2 genes detect less common disease-causing mutations. The recommended first-tier test to screen for NPC is a biochemical test measuring cholesterol esterification coupled with filipin staining on a fibroblast specimen, NIEM / Niemann-Pick Type C Detection, Fibroblasts. Molecular testing provides confirmation of a biochemical diagnosis or a basis for carrier testing of family members. Individuals with abnormal biochemical results are more likely to have 2 identifiable mutations by molecular testing.

Useful For: Second-tier test for confirming a biochemical diagnosis of Niemann-Pick type C (NPC) Carrier testing of individuals with a family history of NPC when an affected individual is not available for testing or disease-causing mutations have not been identified

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations. (1) Variants are classified based on known, predicted, or possible
Nitrogen, Total, 24 Hour, Urine

**Clinical Information:** Nitrogen is a key component of proteins. Nitrogen balance is the difference between the amount of nitrogen ingested and the amount excreted in the urine and feces. A majority of nitrogen is excreted as urea in the urine, however, fecal nitrogen can account for 30% to 50% of total nitrogen excretion. A patient who is in negative nitrogen balance is catabolizing muscle protein to meet the metabolic requirements of the protein catabolism and, therefore, urine and fecal nitrogen may be increased due to stress, physical trauma, surgery, infections, burns, and 11-oxysteroid or thyroxine use. Testosterone and growth hormone have anabolic effects on protein synthesis and may decrease urine and fecal nitrogen. In the course of chronic progressive pancreatitis, as the pancreas is destroyed, serum amylase and lipase may revert to normal. However, excessive fecal nitrogen levels persist and are used as an indicator of pancreatic atrophy.

**Useful For:** Assessing nutritional status (protein malnutrition) Evaluating protein catabolism Determining nitrogen balance, when used in conjunction with 24-hour fecal nitrogen measurement

**Interpretation:** Urinary nitrogen excretion levels within the normal range are indicative of adequate nutrition. Slightly abnormal excretion rates may be a result of moderate stress or complications such as infection or trauma. Significantly abnormal excretion rates may be associated with severe stress due to multiple trauma, head injury, sepsis, or extensive burns. The goal with therapy for a depleted person is a positive nitrogen balance of 4 to 6 g nitrogen/24 hours.

**Reference Values:**
- <16 years: not established
- > or =16 years: 4-20 g/24 hours

**Clinical References:**

Nitrogen, Total, Feces

**Clinical Information:** Nitrogen is a key component of proteins. Nitrogen balance is the difference between the amount of nitrogen ingested and the amount excreted in the urine and feces. A majority of nitrogen is excreted as urea in the urine, however, fecal nitrogen can account for 30% to 50% of total nitrogen excretion. A patient who is in negative nitrogen balance is catabolizing muscle protein to meet the metabolic requirements of the protein catabolism and, therefore, urine and fecal nitrogen may be increased due to stress, physical trauma, surgery, infections, burns, and 11-oxysteroid or thyroxine use. Testosterone and growth hormone have anabolic effects on protein synthesis and may decrease urine and fecal nitrogen. In the course of chronic progressive pancreatitis, as the pancreas is destroyed, serum
amylase and lipase may revert to normal. However, excessive fecal nitrogen levels persist and are used as an indicator of pancreatic atrophy.

**Useful For:** Determining nitrogen balance, when used in conjunction with 24-hour urine nitrogen measurement Assessing nutritional status (protein malnutrition) Evaluating protein catabolism

**Interpretation:** Average fecal nitrogen excretion is approximately 1 to 2 g N/24 hours. Significantly abnormal excretion rates, resulting in negative nitrogen balance, may be associated with severe stress due to multiple trauma, head injury, sepsis, or extensive burns. Elevated values above 2.5 g N/24 hours may be consistent with chronic progressive pancreatitis. The goal with therapy for a depleted person is a positive nitrogen balance of 4 to 6 g N/24 hours.

**Reference Values:**
- <16 years: not established
- > or =16 years: 1-2 g/24 hours

**Clinical References:**

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**FNMR2**

**NMR LipoProfile w/IR Markers**

**Reference Values:**

- **Low:**
  - Moderate: 1000 - 1299
  - Borderline-High: 1300 - 1599
  - High: 1600 - 2000
  - Very High: >2000

- **Moderate:**
  - Lipids LDL-C
  - 0 â€“ 19 years: 0 - 109 mg/dL
  - >19 years: 0 - 99 mg/dL

- **Optimal:**
  - Above Optimal: 100 - 129
  - Borderline: 130 - 159
  - High: 160 - 189
  - Very High: >189

  **Comment:** LDL-C is inaccurate if patient is non-fasting.

- **HDL-C:**
  - >39 mg/dL

- **Triglycerides**
  - 0 â€“ 9 yrs: 0 - 74 mg/dL
  - 10 â€“ 19 yrs: 0 - 89 mg/dL
  - >19 years: 0 - 149 mg/dL

- **Total Cholesterol**
  - 0 â€“ 19 yrs: 100 - 169 mg/dL
>19 years  100 - 199 mg/dL LDL and HDL Particles

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<thead>
<tr>
<th>HDL-P (Total)</th>
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<td>Small LDL-P</td>
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<tr>
<td>LDL Size</td>
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Lower CVD Risk    Higher CVD Risk --> LDL AND HDL PARTICLES Percentile in Reference Population

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<tr>
<th>HDL-P (total)</th>
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<th>75th</th>
<th>50th</th>
<th>25th</th>
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<th>75th</th>
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<tbody>
<tr>
<td></td>
<td>117</td>
<td>527</td>
<td>839</td>
<td>&lt;839</td>
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</table>

>839 LDL Size <--
Large (Pattern A) -->
<-- Small (Pattern B)
-->

- Comment: Small LDL-P and LDL Size are associated with CVD risk, but not after LDL-P is taken into account. These assays were developed and their performance characteristics determined by LipoScience. These assays not been cleared by the US Food and Drug Administration. The clinical utility of these laboratory values have not been fully established. Insulin Resistance and Diabetes Risk

| Large VLDL-P  | nmol/L                     |
| Small LDL-P   | nmol/L                     |
| Large HDL-P   | >or = 4.8 umol/L           |
| VLDL Size     | nm                        |
| LDL Size      | >or= 20.8 nm               |
| HDL Size      | >or= 9.2 nm Insulin Resistance Score  LP-IR Score < or = 45 |

Comment: LP-IR Score is inaccurate if patient is non-fasting. INSULIN RESISTANCE/DIABETES RISK MARKERS Insulin Resistant --> Percentile in Reference Population

<table>
<thead>
<tr>
<th>Large VLDL-P</th>
<th>Low</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
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<tr>
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Small LDL-P Low 25th 50th 75th High

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<td>527</td>
<td>839</td>
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Large HDL-P High 75th 25th Low

>7.3 7.3 4.8 3.1

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<tbody>
<tr>
<td>HDL Size</td>
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<tr>
<td>Insulin Resistance Score</td>
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**LP-IR SCORE**

<table>
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<tr>
<td>High</td>
<td>&gt;63</td>
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</tbody>
</table>

>63 The LP-IR score is a laboratory developed index that has been associated with insulin resistance and diabetes risk and should be used as one component of a physician's clinical assessment. Neither the LP-IR score nor the subclasses listed above have been cleared by the US Food and Drug Administration.

### Nocardia Stain

**Reference Values:**
The laboratory will provide an interpretive report. Reported as positive or negative.

### Non-Seasonal Inhalant Allergen Profile

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
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<th>Class</th>
<th>Interpretation</th>
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<tr>
<td>0</td>
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<td>1</td>
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Clinical Information: Noonan syndrome (NS) is an autosomal dominant disorder of variable expressivity characterized by short stature, congenital heart defects, characteristic facial dysmorphism, unusual chest shape, developmental delay of varying degree, cryptorchidism, and coagulation defects, among other features. Heart defects include pulmonary valve stenosis (20%-50%), hypertrophic cardiomyopathy (20%-30%), atrial septal defects (6%-10%), ventricular septal defects (approximately 5%), and patent ductus arteriosus (approximately 3%). Facial features, which tend to change with age, may include hypertelorism, downward-slanting eyes, epicanthal folds, and low-set and posteriorly rotated ears. Mild mental retardation is seen in up to one-third of adults. The incidence of NS is estimated to be between 1 in 1,000 and 1 in 2,500, although subtle expression in adulthood may cause this number to be an underestimate. NS is genetically heterogeneous, with 4 genes currently associated with the majority of cases: PTPN11, RAF1, SOS1, and KRAS. Heterozygous variants in NRAS, HRAS, BRAF, SHOC2, MAP2K1, MAP2K2, and CBL have also been associated with a smaller percentage of NS and related phenotypes. All of these genes are involved in a common signal transduction pathway known as the Ras-mitogen-activated protein kinase (MAPK) pathway. The MAPK pathway is important for cell growth, differentiation, senescence, and death. Molecular genetic testing of all of the known genes identifies a variant in approximately 75% of affected individuals. NS can be sporadic and due to new variants; however, an affected parent can be recognized in 30% to 75% of families. Some studies have shown that there is a genotype-phenotype correlation associated with NS. An analysis of a large cohort of individuals with NS has suggested that PTPN11 variants are more likely to be found when pulmonary stenosis is present, while hypertrophic cardiomyopathy is commonly associated with RAF1 variants, but rarely associated with PTPN11. A number of related disorders exist that have phenotypic overlap with NS and are caused by variants in the same group of genes. PTPN11 and RAF1 variants have been associated with LEOPARD (lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and deafness) syndrome, an autosomal dominant disorder sharing several clinical features with NS. Variants in BRAF, MAP2K1, MAP2K2, and KRAS have been identified in individuals with cardiofaciocutaneous (CFC) syndrome, a condition involving congenital heart defects, cutaneous abnormalities, Noonan-like facial features, and severe psychomotor developmental delay. Costello syndrome, which is characterized by coarse facies, short stature, distinctive hand posture and appearance, severe feeding difficulty, failure to thrive, cardiac anomalies, and developmental disability has been primarily associated with variants in HRAS. Variation in SHOC2 has been associated with a distinctive phenotype involving features of NS and loose anagen hair. Genes included in the Noonan Syndrome and Related Disorders Multi-Gene Panel Gene Protein Inheritance Disease Association BRAF V-RAF murine sarcoma viral oncogene homolog b1 AD Noonan/CFC/Costello syndrome CBL CAS-BR-M murine ecotropic retroviral transforming sequence homolog AD Noonan syndrome-like disorder HRAS V-HA-RAS Harvey rat sarcoma viral oncogene homolog AD Noonan/CFC/Costello syndrome CBL CAS-BR-M murine ecotropic retroviral transforming sequence homolog AD Noonan syndrome-like disorder HRAS V-HA-RAS Harvey rat sarcoma viral oncogene homolog AD Costello syndrome KRAS V-KI-RAS Kirsten rat sarcoma viral oncogene homolog AD Noonan/CFC/Costello syndrome MAP2K1 Mitogen-activated protein kinase kinase 1 AD Noonan/CFC MAP2K2 Mitogen-activated protein kinase kinase 2 AD Noonan/CFC NRAS Neuroblastoma ras viral oncogene homolog AD Noonan syndrome PTPN11 Protein-tyrosine phosphatase, nonreceptor-type, 11
AD Noonan/CFC/LEOPARD syndrome RAF1 V-raf-1 murine leukemia viral oncogene homolog 1 AD Noonan/LEOPARD syndrome SHOC2 Suppressor of clear, c. Elegans, homolog of AD Noonan-syndrome like with loose anagen hair SOS1 Son of sevenless, drosophila, homolog 1 AD Noonan-syndrome like with loose anagen hair

Abbreviations: Autosomal dominant (AD)

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of Noonan syndrome (NS) or related disorders. Establishing a diagnosis of a NS or related disorders, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved. Identifying variants within genes known to be associated with increased risk for disease features allowing for predictive testing of at-risk family members.

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values: An interpretive report will be provided.

Interpretation: A positive result indicates that nucleic acid (RNA) from norovirus genogroups 1 and/or 2 was present in the clinical specimen. A negative result suggests that nucleic acid (RNA) from norovirus genogroups 1 or 2 was absent in the clinical specimen.

Reference Values:
Negative


Northeast Regional Allergen Profile

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.

Nortriptyline, Serum

**Clinical Information:** Nortriptyline is a tricyclic antidepressant used for treatment of endogenous depression. It also is a metabolite of the antidepressant amitriptyline. Nortriptyline is used when its stimulatory side effect is considered to be of clinical advantage; amitriptyline is used when the side effect of mild sedation is desirable. Nortriptyline is unique among the antidepressants in that its blood level exhibits the classical therapeutic window effect; blood concentrations above or below the therapeutic window correlate with poor clinical response. Thus, therapeutic monitoring to ensure that the blood level is within the therapeutic window is critical to accomplish successful treatment with this drug. Like amitriptyline, nortriptyline can cause major cardiac toxicity when the concentration is above 500 ng/mL, characterized by QRS widening, which leads to ventricular tachycardia and asystole. In some patients, toxicity may manifest at lower concentrations.

**Useful For:** Monitoring serum concentration during therapy Evaluating potential toxicity The test may also be useful to evaluate patient compliance

**Interpretation:** Most individuals display optimal response to nortriptyline with serum levels of 70 to 170 ng/mL. Risk of toxicity is increased with nortriptyline levels above 500 ng/mL. Some individuals may respond well outside of this range, or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next dose).

**Reference Values:**
Therapeutic concentration: 70-170 ng/mL
Note: Therapeutic ranges are for specimens drawn at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.

**Clinical References:**

NOTCH3 (CADASIL) Sequencing Test

**Clinical Information:** Detects sequence variants in the NOTCH3 gene in patients with CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy).

**Reference Values:**
A final report will be attached in MayoAccess.

NR4A3 (9q22.33) Rearrangement, FISH, Tissue

**Clinical Information:** The gene NR4A3 is often altered in patients with extraskeletal myxoid chondrosarcomas (EMC). Rearrangement of the NR4A3 gene region may be involved with up to 4 partner genes as a pathway to EMC. FISH analysis allows for the detection of rearrangement of the NR4A3 gene region.

**Useful For:** Identifying NR4A3 gene rearrangements in patients with extraskeletal myxoid chondrosarcoma (EMC)

**Interpretation:** A positive result with the NR4A3 probe is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result of NR4A3 suggests inactivating structural alterations of the NR4A3 gene region at 9q22.33. A negative result suggests no structural alterations of the locus.
Reference Values:
An interpretive report will be provided.


NT-Pro B-Type Natriuretic Peptide (BNP), Serum

Clinical Information: B-type natriuretic peptide (brain natriuretic peptide: BNP) is a small, ringed peptide secreted by the heart to regulate blood pressure and fluid balance. This peptide is stored in and secreted predominantly from membrane granules in the heart ventricles in a pro form (proBNP). Once released from the heart in response to ventricle volume expansion or pressure overload, the N-terminal (NT) piece of 76 amino acids (NT-proBNP) is rapidly cleaved by the enzymes corin and furin to release the active 32-amino acid peptide (BNP). Both BNP and NT-proBNP are markers of atrial and ventricular distension due to increased intracardiac pressure. The New York Heart Association (NYHA) developed a 4-stage functional classification system for congestive heart failure (CHF) based on the severity of the symptoms. Studies have demonstrated that the measured concentrations of circulating BNP and NT-proBNP increase with the severity of CHF based on the NYHA classification.

Useful For: Aids in the diagnosis of congestive heart failure

Interpretation: Under 50 years of age: N-terminal pro brain natriuretic peptide (NT-proBNP) values below 300 pg/mL have a 99% negative predictive value for excluding acute congestive heart failure (CHF). A cutoff of 1,200 pg/mL for patients with an estimated glomerular filtration rate (eGFR) below 60 yields a diagnostic sensitivity and specificity of 89% and 72% for acute CHF. NT-proBNP values greater than 450 pg/mL are consistent with CHF in adults under 50 years of age: NT-proBNP values below 300 pg/mL have a 99% negative predictive value for excluding acute CHF. A cutoff of 1,200 pg/mL, for patients with an eGFR below 60 yields a diagnostic sensitivity and specificity of 89% and 72% for acute CHF. A diagnostic NT-proBNP cutoff of 900 pg/mL has been suggested in adults 50 to 75 years of age in the absence of renal failure. Over 75 years of age: NT-proBNP values below 300 pg/mL have a 99% negative predictive value for excluding acute CHF. A cutoff of 1,200 pg/mL for patients with an eGFR below 60 yields a diagnostic sensitivity and specificity of 89% and 72% for acute CHF. A diagnostic NT-proBNP cutoff of 1,800 pg/mL has been suggested in adults over 75 years of age in the absence of renal failure. NT-Pro BNP levels are loosely correlated with New York Heart Association (NYHA) functional class (see Table). Interpretive Levels for CHF Functional Class 5th to 95th Percentile Median I 31-1,110 pg/mL 377 pg/mL II 55-4,975 pg/mL 1,223 pg/mL III 77-26,916 pg/mL 3,130 pg/mL IV * * * In a Mayo Clinic study of 75 patients with CHF, only 4 were characterized as Class IV. Accordingly, range and median are not provided.

Reference Values:
Males
< or =45 years: 10-51 pg/mL
46 years: 10-53 pg/mL
47 years: 10-55 pg/mL
48 years: 10-56 pg/mL
49 years: 10-58 pg/mL
50 years: 10-59 pg/mL
51 years: 10-61 pg/mL
52 years: 10-62 pg/mL
53 years: 10-64 pg/mL
54 years: 10-67 pg/mL
55 years: 10-68 pg/mL
56 years: 10-70 pg/mL
57 years: 10-71 pg/mL
58 years: 10-73 pg/mL
59 years: 10-76 pg/mL
60 years: 10-77 pg/mL

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<td>&gt;83</td>
<td>10-138</td>
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Females

- < or =46 years: 10-140 pg/mL
- 47 years: 10-141 pg/mL
- 48 years: 10-144 pg/mL
- 49 years: 10-146 pg/mL
- 50 years: 10-149 pg/mL
- 51 years: 10-150 pg/mL
- 52 years: 10-152 pg/mL
- 53 years: 10-155 pg/mL
- 54 years: 10-157 pg/mL
- 55 years: 10-160 pg/mL
- 56 years: 10-162 pg/mL
- 57 years: 10-166 pg/mL
- 58 years: 10-168 pg/mL
- 59 years: 10-171 pg/mL
- 60 years: 10-173 pg/mL
- 61 years: 10-177 pg/mL
- 62 years: 10-179 pg/mL
- 63 years: 10-183 pg/mL
- 64 years: 10-185 pg/mL
- 65 years: 10-189 pg/mL
- 66 years: 10-193 pg/mL
- 67 years: 10-196 pg/mL
- 68 years: 10-199 pg/mL
- 69 years: 10-202 pg/mL
- 70 years: 10-206 pg/mL
- 71 years: 10-210 pg/mL
- 72 years: 10-214 pg/mL
- 73 years: 10-218 pg/mL
- 74 years: 10-222 pg/mL
- 75 years: 10-227 pg/mL
- 76 years: 10-230 pg/mL
- 77 years: 10-235 pg/mL
- 78 years: 10-239 pg/mL
79 years: 10-244 pg/mL
80 years: 10-248 pg/mL
81 years: 10-253 pg/mL
82 years: 10-258 pg/mL
> or =83 years: 10-263 pg/mL


NTXPR
61656

NTX-Telopeptide, Urine

Clinical Information: Human bone is continuously remodeled through a process of osteoclast-mediated bone formation and resorption. This process can be monitored by measuring serum and urine markers of bone formation and resorption. Approximately 90% of the organic matrix of bone is type I collagen, a helical protein that is cross-linked at the N- and C-terminal ends of the molecule. The amino acid sequences and orientation of the cross-linked alpha 2 N-telopeptide of type 1 collagen make it a specific marker of human bone resorption. N-terminal telopeptide (NTx) molecules are mobilized from bone by osteoclasts and subsequently excreted in the urine. Elevated levels of NTx indicate increased bone resorption. Bone turnover markers are physiologically elevated during childhood, growth, and during fracture healing. The elevations in bone resorption markers and bone formation markers are typically balanced in these circumstances and of no diagnostic value. By contrast, abnormalities in the process of bone remodeling can result in changes in skeletal mass and shape. Many diseases, in particular hyperthyroidism, all forms of hyperparathyroidism, most forms of osteomalacia and rickets (even if not associated with hyperparathyroidism), hypercalcemia of malignancy, Paget disease, multiple myeloma, and bony metastases, as well as various congenital diseases of bone formation and remodeling can result in accelerated and unbalanced bone turnover. Unbalanced bone turnover, usually without increase in bone turnover, is also found in age-related and postmenopausal osteopenia and osteoporosis. Disease-associated bone turnover abnormalities should normalize in response to effective therapeutic interventions, which can be monitored by measurement of serum and urine bone resorption and formation markers.

Useful For: As an adjunct in the diagnosis of medical conditions associated with increased bone turnover Monitoring effectiveness of antiresorptive therapy in patients treated for osteopenia, osteoporosis, Paget disease, or other metabolic bone disorders

Interpretation: Elevated levels of N-terminal telopeptide (NTx) indicate increased bone resorption. Most patients with osteopenia or osteoporosis have low, but unbalanced, bone turnover, with bone resorption dominating over bone formation. While this may result in mild elevations in bone turnover markers in these patients, finding significantly elevated urine NTx levels is atypical. Therefore, if levels are substantially elevated above the young adult reference range (> 1.5- to 2-fold), the likelihood of coexisting osteomalacia, or of an alternative diagnosis as described in the Clinical Information section, should be considered. When alternative causes for elevated NTx have been excluded in a patient with osteopenia/osteoporosis, the patient must be considered at increased risk for accelerated progression of osteopenia/osteoporosis. A 30% or greater reduction in this resorption marker 3 to 6 months after initiation of therapy indicates a probably adequate therapeutic response. The Negotiated Rulemaking Committee of HCFA also recommends: "Because of significant specimen-to-specimen collagen crosslink physiologic variability (15%-20%), current recommendations for appropriate utilization include: 1 or 2 baseline assays from specified urine collections on separate days; followed by a repeat assay about 3 months after starting antiresorptive therapy; followed by a repeat assay in 12 months; thereafter not more than annually, if medically necessary."

Reference Values:
All units are reported in nmol Bone Collagen Equivalents/mmol creatinine.
Adult (> or =18 years of age)
Males:
21-83 nmol BCE/mmol creatinine

Females:
Premenopausal: 17-94 nmol BCE/mmol creatinine
Postmenopausal: 26-124 nmol BCE/mmol creatinine

Pediatric
Males:
Tanner Stage I: 55-508 nmol BCE/mmol creatinine
Tanner Stage II: 21-423 nmol BCE/mmol creatinine
Tanner Stage III: 27-462 nmol BCE/mmol creatinine
Tanner Stage IV: <609 nmol BCE/mmol creatinine
Tanner Stage V: <240 nmol BCE/mmol creatinine

Females:
Tanner Stage I: 6-662 nmol BCE/mmol creatinine
Tanner Stage II: 193-514 nmol BCE/mmol creatinine
Tanner Stage III: 13-632 nmol BCE/mmol creatinine
Tanner Stage IV: <389 nmol BCE/mmol creatinine
Tanner Stage V: <132 nmol BCE/mmol creatinine

Clinical References:

NPM1
Nucleophosmin (NPM1) Mutation Analysis

Clinical Information: Acute myelogenous leukemia (AML) is a heterogenous group of neoplasms. While cytogenetic aberrations detected at the time of diagnosis are the most commonly used prognostic feature, approximately 20% of AML cases show a normal karyotype, which is considered an intermediate-risk feature. Within this group, FLT3 mutations are considered indicators of poor prognosis. However, in the absence of a FLT3 mutation, the presence of a nucleophosmin (NPM1) mutation is associated with a more favorable prognosis. Thus, in patients with newly diagnosed AML, those with normal karyotype, no FLT3 mutation, and a NPM1 mutation are considered to have a better prognosis than patients in the same group with neoplasms lacking a NPM1 mutation.

Useful For: As a prognostic indicator in patients with newly diagnosed acute myelogenous leukemia with normal karyotype and no FLT3 mutation

Interpretation: The assay will be interpreted as positive, low positive, or negative for the NPM1 mutation. In patients with newly diagnosed acute myelogenous leukemia, a normal karyotype, and no FLT3 mutation, the presence of NPM1 mutation is an indicator of a more favorable prognosis.

Reference Values:
An interpretive report will be provided.

Clinical References:
**NUT Immunostain, Technical Component Only**

**Clinical Information:** Nuclear protein in testis (NUT) is normally confined to the germ cells of the testis and ovary. A recently recognized cancer is NUT midline carcinoma (NMC), defined by the presence of chromosomal rearrangements involving the NUT gene on chromosome 15q14. NMCs are aggressive and highly lethal carcinomas, and are very difficult to discern from other poorly differentiated carcinomas by morphology alone.

**Useful For:** Aiding in the diagnosis of nuclear protein in testis (NUT) midline carcinoma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**NUT1F**

**NUTM1 (15q14) Rearrangement, FISH, Tissue**

**Clinical Information:** Nuclear protein in testis (NUT) midline carcinomas (NMC) are rare aggressive tumors with rapid onset. Although NMC has been described in several anatomic sites, it is commonly observed in the head, neck, or thorax. These tumors are poorly differentiated and defined by rearrangement of the NUTM1 gene on chromosome 15q14. In the majority of cases, NUTM1 is rearranged in an apparently balanced translocation with the BRD4 gene on chromosome 19p13.1; however, other partners for NUTM1 rearrangement have been reported. NUTM1 rearrangement has not been identified in other midline malignancies. Therefore, a separation of NUTM1, in the proper clinical and histologic context, is diagnostic for NMC and can be confirmed by FISH with NUT break-apart probes.

**Useful For:** Identifying NUTM1 gene rearrangements in patients with NUT midline carcinoma to aid in confirming or excluding the diagnosis

**Interpretation:** The presence of NUTM1 rearrangement confirms the diagnosis of nuclear protein in testis midline carcinomas (NMC) in the proper clinical and histologic context. The absence of NUTM1 rearrangement rules out the diagnosis of NMC in the proper clinical and histologic context. A positive result is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result suggests rearrangement of the NUTM1 locus which, in conjunction with the proper clinical and histologic features, is diagnostic of NMC. A negative result suggests no rearrangement of the NUTM1 gene region at 15q14. A confirmed diagnosis of NMC results in specific clinical management that may be distinct from the management of other carcinomas.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
2. Ziai
Nutmeg, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing a diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms Identifying allergens responsible for anaphylaxis, confirming sensitization to particular allergens prior to beginning immunotherapy, and investigating the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Allergy PEAN:**

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<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>0/1</td>
<td>0.10-0.34</td>
<td>Borderline/Equivocal</td>
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<tr>
<td>1</td>
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**FNGPGL**

**Nuts and Grains Panel IgG Reference Values:**

Almond Food IgG
Food-specific IgG tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization to the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**FOAKE 57999**

**Oak Live (Quercus virginiana) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal/Borderline 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 High Positive 4 17.50 â€“ 49.99 Very High Positive 5 50.00 â€“ 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**

<0.35 kU/L

**FROE 57907**

**Oak Red (Quercus rubra) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

**OAK 82673**

**Oak, IgE**

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization to the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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FOATG

Oat IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.
Oat, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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Reference values apply to all ages.


Occupational Panel # 2

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
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**OCT2 Immunostain, Technical Component Only**

**Clinical Information:** OCT-2 is a transcription factor that binds to the octamer motif of the immunoglobulin gene promoter, recruits the coactivator BOB.1, and activates immunoglobulin gene transcription. OCT-2 is variably expressed in germinal center B cells, weakly expressed in mantle zone B cells, and weakly to moderately expressed in plasma cells. The protein is localized to the nuclear compartment. Expression of BOB.1, OCT-2, and PU.1 transcription factors are often down regulated in classical Hodgkin lymphoma. OCT-2 is overexpressed in lymphocyte-predominant (LP) cells of nodular LP Hodgkin lymphoma. These properties can be useful in the diagnosis of lymphoma.

**Useful For:** Classification of lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

OCT4
70523

OCT3/4 Immunostain, Technical Component Only

Clinical Information: Octamer-binding transcription factor 3/4 (OCT4), also known as POU5F1, is a transcription factor expressed by embryonal stem cells and germ cells. Staining for OCT4 can aid in the diagnosis of testicular or ovarian germ cell tumors; it is highly specific for germ cell neoplasia, especially seminomas. Alternative splicing produces 2 mRNA variants from the POU5F1 gene, originally named OCT3A and OCT3B, thus the OCT3/4 name.

Useful For: Aids in the identification of germ cell tumors

Interpretation: The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


OCTO
82820

Octopus, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflamatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L  Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


FLNZ 91129

Olanzapine (Zyprexa)
Reference Values:
Reference Range: 10.0 – 80.0 ng/mL

Expected steady state concentrations in patients on recommended daily dosages:
10.0 – 80.0 ng/mL
Plasma concentrations of olanzapine greater than 9.0 ng/mL have been associated with therapeutic effect.
Toxic range has not been established.

OLIG2 71357

OLIG2 Immunostain, Technical Component Only
Clinical Information: Oligodendrocyte transcription factor 2 (OLIG2) is a transcription factor that participates in oligodendrocyte and motor neuron differentiation. During embryogenesis OLIG2 promotes the growth of motor neuron progenitor cells. OLIG2 expression decreases upon further neuronal differentiation. OLIG2 is also involved in oligodendrocyte differentiation where expression remains present in mature glial cells. In gliomas, OLIG2 represses the p53 tumor suppressor pathway, thereby contributing to glioma progression.
Useful For: Distinguishing gliomas from neurocytomas and ependymomas
Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.
Oligoclonal Banding, Serum and Spinal Fluid

Clinical Information: The diagnosis of multiple sclerosis (MS) is dependent on clinical, radiological, and laboratory findings. The detection of increased intrathecal immunoglobulin (Ig) synthesis is the basis for current diagnostic laboratory tests for MS. These tests include the cerebrospinal fluid (CSF) IgG index and CSF oligoclonal band (OCB) detection. Abnormal CSF IgG indexes and OCB patterns have been reported in 70% to 80% of MS patients. At least 1 of these tests has been reported to be positive in 90% of MS patients when both tests are performed. Newer methodologies for OCB detection have been reported to be more sensitive, with sensitivities of 90% to 95% in CSF from MS patients. Increased intrathecal Ig synthesis may occur in other inflammatory CSF diseases and, therefore, this assay is not specific for MS (specificity = 95%).

Useful For: Diagnosis of multiple sclerosis; especially useful in patients with equivocal clinical presentation and radiological findings

Interpretation: A finding of 4 or more cerebrospinal fluid (CSF)-specific bands (i.e., bands that are present in CSF but are absent in serum) is consistent with multiple sclerosis. The presence of oligoclonal band is unrelated to disease activity.

Reference Values:
CSF Olig Bands Interpretation: <4 bands


Oligosaccharide Screen, Random, Urine

Clinical Information: Oligosaccharidoses are characterized by the abnormal accumulation of incompletely degraded oligosaccharides in cells and tissues and the corresponding increase of related free oligosaccharides in the urine. Clinical features of oligosaccharidoses often overlap; therefore, urine screening is an important tool in the initial workup for these disorders. Enzyme or molecular analysis is required to make a definitive diagnosis.

Useful For: Screening for possible oligosaccharidoses

Interpretation: This is a screening test; not all oligosaccharidoses are detected. The resulting excretion profile may be characteristic of a specific disorder; however, abnormal results require confirmation by enzyme assay or molecular genetic testing. When abnormal results are detected with characteristic patterns, a detailed interpretation is given, including an overview of results and significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional confirmatory studies (enzyme assay, molecular genetic analysis).

Reference Values:
Only orderable as part of a profile. See LYSDU / Lysosomal Storage Disorders Screen, Urine.

For information regarding oligosaccharides, see OLIGU / Oligosaccharide Screen, Urine.

Oligosaccharide Screen, Urine

Clinical Information: The oligosaccharidoses (glycoproteinoses) are a subset of lysosomal storage disorders caused by the deficiency of any one of the lysosomal enzymes involved in the degradation of complex oligosaccharide chains. They are characterized by the abnormal accumulation of incompletely degraded oligosaccharides in cells and tissues and the corresponding increase of related free oligosaccharides in the urine. Clinical diagnosis is difficult due to the similarity of clinical features across disorders and their variability. Clinical features can include bone abnormalities, coarse facial features, corneal cloudiness, organomegaly, muscle weakness, hypotonia, developmental delay, and ataxia. Age of onset ranges from early infancy to adult and can even present prenatally. This is the recommended test for the initial workup of a suspected oligosaccharidosis disorder. The oligosaccharidoses in this subset of lysosomal storage disorders and detected by this assay are alpha-mannosidosis, beta-mannosidosis, aspartylglucosaminuria, fucosidosis, Schindler disease, GM1 gangliosidosis, Sandhoff disease, sialidosis, galactosialidosis, mucolipidosis types II and III, mucopolysaccharidosis IVB (Morquio B), and Pompe disease (see table). LYSDU/Lysosomal Storage Disorders Screen, Urine includes analysis of urine oligosaccharides and is the recommended screening test for the initial workup of a suspected lysosomal storage disorder. Conditions Identifiable By Method Disorder Onset Gene Enzyme Deficiency Worldwide Incidence Alpha-mannosidosis Prenatal (type III) Infancy (type I) Juvenile/Adult (type II) MAN2B1 Alpha-mannosidase 1:500,000 Phenotype: continuum of clinical features ranging from severe and rapidly progressive disease to a milder and more slowly progressive course. Prenatal onset (type III) manifests as prenatal loss or early death from progressive neurodegeneration. Infantile onset (type I) is characterized by rapidly progressive mental retardation, hepatosplenomegaly, and severe dysostosis multiplex. Type II is milder and slower progressing with survival into adulthood. Beta-mannosidosis Infancy to juvenile MANBA Beta-mannosidase <100 patients described Phenotype: clinical features vary in severity and may include intellectual disability, respiratory infections, hearing loss, hypotonia, peripheral neuropathy, and behavioral issues. Aspartylglucosa-minuria Early childhood AGA Aspartylglucosaminidase 1:2,000,000 higher incidence in Finland approx 1:17,000 Phenotype: normal appearing at birth followed by progressive neurodegeneration at 2-4 years, frequent respiratory infections, coarse features, thick calvarium, and osteoporosis. Slowly progressive mental decline into adulthood. Alpha-fucosidosis Infancy to early childhood FUCA1 Alpha-fucosidase <100 patients described Phenotype: continuum within a wide spectrum of severity; clinical features include neurodegeneration, coarse facial features, growth delay, recurrent infections, dysostosis multiplex, angiookeratoma, and elevated sweat chloride Schindler disease Infancy (type I) Early childhood (type III) Adult (type II) NAGA Alpha-N-Acetyl-galactosaminidase <30 patients described Phenotype: continuum of clinical features ranging from severe and rapidly progressive disease to a milder and more slowly progressive course; infantile onset (type I) is characterized by rapidly progressive neurodegeneration. Type II is adult onset characterized by angiookeratoma and mild cognitive impairment, and type III is an intermediate and variable form ranging from seizures and psychomotor delay to milder autistic features. GM1 gangliosidosis Infancy (type I) Late infantile/juvenile (type II) Adult (type III) GLB1 Beta-galactosidase (Beta-Gal) 1:200,000 Phenotype: continuum of clinical features ranging from severe and rapidly progressive disease to a milder and more slowly progressive course; infantile onset (type I) is characterized by early developmental delay/arrest followed by progressive neurodegeneration, skeletal dysplasia, facial coarseness, hepatosplenomegaly, and macular cherry red spot. Later onset forms (types II and III) are milder and observed as progressive neurologic disease and vertebral dysplasia. Adult onset presents mainly with dystonia. GM2 gangliosidosis variant 0 (Sandhoff disease) Early infancy to juvenile or adult HEXB Beta-hexosaminidase A and B 1:400,000 Phenotype: infantile onset is characterized by rapidly progressive neurodegeneration, exaggerated startle reflex, "cherry red spot". Milder later-adult onset forms of the disease exist presenting with neurological problems such as ataxia, dystonia, spinal-cerebellar degeneration, and behavior changes. Sialidosis (ML I) Early adulthood (type I) Earlier for congenital, infantile, and juvenile forms (type II) NEU1 Alpha-neuraminidase (Neu) <30 patients described Phenotype: continuum of clinical features ranging from severe disease (type II) to a milder and more slowly progressive course (type I). Clinical features range from early developmental delay, coarse
facial features, short stature, dysostosis multiplex, and hepatosplenomegaly to late onset cherry-red spot myoclonus syndrome. Seizures, hyperreflexia, and ataxia have been reported in more than 50% of later onset patients. A congenital form of the disease has been reported in which patients present with fetal hydrops or neonatal ascites. Galactosialidosis Early infancy, late infancy or early adult CTSA Cathepsin A causing secondary deficiencies in Beta-Gal and Neu <30 patients described Phenotype: continuum of clinical features ranging from severe and rapidly progressive disease to a milder and more slowly progressive course; clinical features of the early infantile type include fetal hydrops, edema, ascites, visceromegaly, dysostosis multiplex, coarse facies, and cherry red spot. The majority of patients have milder presentations, which include ataxia, myoclonus, angiokeratoma, cognitive and neurologic decline. Mucolipidosis II-alpha/-beta (I-cell) Mucolipidosis III-alpha/-beta and III-gamma (pseudo-Hurler Polydystrophy) Early infancy Early childhood, may live well into adulthood GNPTAB(alpha/beta) GNPTG (gamma) N-acetylglucosaminyl-1-phosphotransferase deficiency causing secondary intracellular deficiency of multiple enzyme activities 1:300,000 Phenotype: I-cell resembles Hurler with short stature and skeletal anomalies, but presents earlier, is more severe, and can include cardiomyopathy and coronary artery disease. Pseudo-Hurler polydystrophy is milder and later presenting. Mucopoly-saccharidosis IVB (Morquio B) Infancy to adult GLB1 Beta-galactosidase (Beta-Gal) 1:75,000 N. Ireland 1:640,000 W. Australia Phenotype: progressive condition that largely affects the skeletal system. Features include short-trunk dwarfism, skeletal (spondyloepiphyseal) dysplasia, fine corneal deposits, and preservation of intelligence. Pompe disease (Glycogen storage disease type II) Early infancy Late onset (childhood-adult) GAA Alpha-glucosidase 1:40,000 Phenotype: infantile onset is characterized by prominent cardiomegaly, hepatomegaly, hypotonia, and weakness. Later onset forms present with proximal muscle weakness and respiratory insufficiency.

**Useful For:** Screening for possible oligosaccharidoses

**Interpretation:** This is a screening test; not all oligosaccharidoses are detected. The resulting excretion profile may be characteristic of a specific disorder; however, abnormal results require confirmation by enzyme assay or molecular genetic testing. When abnormal results are detected with characteristic patterns, a detailed interpretation is given, including an overview of results and significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional confirmatory studies (enzyme assay, molecular genetic analysis).

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FOLBG 57671**

**Olive Black IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.
**Olive Russian (Elaeagnus angustifolia) IgE**

**Interpretation:**
- Class IgE (kU/L)
- Comment
- 0 <0.10 Negative
- 0.10 - 0.34 Equivocal
- 0.35 - 0.69 Low Positive
- 0.70 - 3.4 Moderate Positive
- 3.5 - 17.4 High Positive
- 4 5 6 17.5 - 49.9 50.0 - 99.9 > or = 100 Very High Positive

**Reference Values:**
- <0.35 kU/L

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**Olive Tree, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
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<td>1</td>
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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**OncoHeme Next-Generation Sequencing (NGS), Hematologic Neoplasms**

**Clinical Information:** Next-generation sequencing (NGS) is a rapidly evolving and complex methodology that can interrogate multiple regions of genomic tumor DNA in a single assay. Many hematologic neoplasms are characterized by morphologic or phenotypic similarities, but can have characteristic somatic mutations in many genes. In addition, many myeloid neoplasms lack a clonal cytogenetic finding at diagnosis (normal karyotype) but can be diagnosed and classified according to the gene mutation profile. The presence and pattern of gene mutations can provide critical diagnostic, prognostic, and sometimes therapeutic information for the managing physicians.

**Useful For:** Evaluation of hematologic neoplasms at the time of diagnosis, to assist in appropriate classification and prognosis. Determining the presence of new clinically important gene mutation changes at relapse.

**Interpretation:** Mutations (gene alterations) identified, if present. An interpretive report will be
Reference Values:
An interpretive report will be provided.


Onion IgG
Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Onion, IgE
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative

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**OPTMX 62736 Opiate Confirmation, Chain of Custody, Meconium**

**Clinical Information:** Opiates are naturally occurring alkaloids that are derived from the opium poppy and demonstrate analgesic effects. Opioids are derived from natural and semisynthetic alkaloids of opium or synthetic compounds(1): -Codeine is a naturally occurring opioid agonist often incorporated into formulations along with acetaminophen or aspirin to increase its analgesic effect.(2) Codeine is metabolized to morphine and subsequently undergoes glucuronidation and sulfation.

-Morphine is an opioid receptor agonist that is used for major pain analgesia.(2) It has been shown to distribute widely into many fetal tissues,(4) and has been detected in meconium. -Hydrocodone is a semisynthetic analgesic derived from codeine. Hydrocodone is 6 times more potent than codeine and is prescribed for treatment of moderate-to-moderately severe pain.(2) Hydrocodone undergoes O-demethylation in vivo, forming hydromorphone. -Hydromorphone, a semisynthetic derivative of morphine, is an opioid analgesic. It is 7 to 10 times more potent than morphine, its addiction liability is similar to morphine.(2) -Oxycodone, a semisynthetic narcotic derived from thebaine. It is metabolized by O-demethylation, forming oxymorphine.(2) -Oxymorphone is a semisynthetic opioid derivative of thebaine and is indicated for moderate-to-severe pain.(2) -Heroin, a semisynthetic derivative of morphine, is rapidly deacetylated in vivo to the active metabolite 6-monoacetlymorphine (6-MAM), which is further hydrolyzed to morphine.(2) Opiates have been shown to readily cross the placenta and distribute widely into many fetal tissues. Opiate use by the mother during pregnancy increases the risk of prematurity and small size for gestational age. Furthermore, heroin-exposed infants exhibit an early onset of withdrawal symptoms compared to methadone-exposed infants. These infants demonstrate a variety of symptoms including irritability, hypertonia, wakefulness, diarrhea, yawning, sneezing, increased hiccups, jitteriness, excessive sucking, and seizures. Long-term intrauterine drug exposure may lead to abnormal neurocognitive and behavioral development as well as an increased risk of sudden infant death syndrome. The disposition of opiates and opioids in meconium, the first fecal material passed by the neonate, is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing of amniotic fluid. The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation, and slowly moves into the colon by the 16th week of gestation. Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection of maternal prenatal opiate/opioid use up to 5 months before birth Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures
that the test results are appropriate for legal proceedings.

**Interpretation:** The presence of any of the following opiates (codeine, morphine, hydrocodone, hydromorphone, oxycodone, oxymorphone) at \( > \text{or} \geq 50 \text{ ng/g} \) or 6-monoacetlymorphine at \( > \text{or} \geq 10 \text{ ng/g} \) indicates the newborn was exposed to opiates/opioids during gestation.

**Reference Values:**

- Negative
- Positives are reported with a quantitative LC-MS/MS result.
- Cutoff concentrations
  - Codeine by LC-MS/MS: 50 ng/mL
  - Hydrocodone by LC-MS/MS: 50 ng/mL
  - Hydromorphone by LC-MS/MS: 50 ng/mL
  - Morphine by LC-MS/MS: 50 ng/mL
  - Oxycodone by LC-MS/MS: 50 ng/mL
  - Oxymorphone by LC-MS/MS: 50 ng/mL

**Clinical References:**

**OPATM 84326**

**Opiate Confirmation, Meconium**

**Clinical Information:** Opiates are naturally occurring alkaloids that are derived from the opium poppy and demonstrate analgesic effects. Opioids are derived from natural and semisynthetic alkaloids of opium or synthetic compounds(1): - Codeine is a naturally occurring opioid agonist often incorporated into formulations along with acetaminophen or aspirin to increase its analgesic effect.(2) Codeine is metabolized to morphine and subsequently undergoes glucuronidation and sulfation. - Morphine is an opioid receptor agonist that is used for major pain analgesia.(2) It has been shown to distribute widely into many fetal tissues,(4) and has been detected in meconium. - Hydrocodone is a semisynthetic analgesic derived from codeine. Hydrocodone is 6 times more potent than codeine and is prescribed for treatment of moderate-to-moderately severe pain.(2) Hydrocodone undergoes O-demethylation in vivo, forming hydromorphone. - Hydromorphone, a semisynthetic derivative of morphine, is an opioid analgesic. It is 7 to 10 times more potent than morphine, its addiction liability is similar to morphine.(2) - Oxycodone, a semisynthetic narcotic derived from thebaine. It is metabolized by O-demethylation, forming oxymorphone.(2) - Oxymorphone is a semisynthetic opioid derivative of thebaine and is indicated for moderate-to-severe pain.(2) - Heroin, a semisynthetic derivative of morphine, is rapidly deacetylated in vivo to the active metabolite 6-monooacetlymorphine (6-MAM), which is further hydrolyzed to morphine.(2) Opiates have been shown to readily cross the placenta and distribute widely into many fetal tissues. Opiate use by the mother during pregnancy increases the risk of prematurity and small size for gestational age. Furthermore, heroin-exposed infants exhibit an early onset of withdrawal symptoms compared to methadone-exposed infants. These infants demonstrate a variety of symptoms including irritability, hypertonia, wakefulness, diarrhea, yawning, sneezing, increased hiccups, jitteriness, excessive sucking, and seizures. Long-term intrauterine drug exposure may lead to abnormal neurocognitive and behavioral development as well as an increased risk of sudden infant death syndrome. The disposition of opiates and opioids in meconium, the first fecal material passed by the neonate, is not well understood.
The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposition from bile or through swallowing of amniotic fluid. The first evidence of meconium in the fetal intestine appears at approximately the tenth to twelfth week of gestation, and slowly moves into the colon by the sixteenth week of gestation. Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.

**Useful For:** Detection of maternal prenatal opiate/opioid use up to 5 months before birth

**Interpretation:** The presence of any of the following opiates (codeine, morphine, hydromorphone, oxycodone, oxymorphone) at 50 ng/g or greater or 6-monoacetlymorphine at 10 ng/g or greater indicates the newborn was exposed to opiates/opioids during gestation.

**Reference Values:**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Cutoff Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine by LC-MS/MS</td>
<td>50 ng/g</td>
</tr>
<tr>
<td>Hydrocodone by</td>
<td>50 ng/g</td>
</tr>
<tr>
<td>LC-MS/MS</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone by</td>
<td>50 ng/g</td>
</tr>
<tr>
<td>LC-MS/MS</td>
<td></td>
</tr>
<tr>
<td>Morphine by</td>
<td>50 ng/g</td>
</tr>
<tr>
<td>LC-MS/MS</td>
<td></td>
</tr>
<tr>
<td>Oxycodone by</td>
<td>50 ng/g</td>
</tr>
<tr>
<td>LC-MS/MS</td>
<td></td>
</tr>
<tr>
<td>Oxymorphone by</td>
<td>50 ng/g</td>
</tr>
<tr>
<td>LC-MS/MS</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical References:**


**Opiates Confirmation, Chain of Custody, Urine**

**Clinical Information:** Codeine is converted by hepatic metabolism to morphine and norcodeine with a half-life of 2 to 4 hours. If codeine is ingested, the ratio of codeine to morphine generally exceeds 1.0 in urine during the first 24 hours. The ratio may fall below 1.0 after 24 hours; and after 30 hours, only morphine may be detected. Morphine is a naturally occurring narcotic analgesic obtained from the poppy plant, Papaver somniferum. Morphine is converted by hepatic metabolism to normorphine with a half-life of 2 to 4 hours. The presence of morphine in urine can indicate exposure to morphine, heroin, or codeine within 2 to 3 days. Ingestion of bakery products containing poppy seeds can also cause morphine to be excreted in urine. If excessively large amounts are consumed, this can result in urine morphine concentrations up to 2,000 ng/mL for a period of 6 to 12 hours after ingestion. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation, and 6-keto reduction to the 6-beta hydroxymetabolites. Hydromorphine and norhydrocodone are both metabolites of hydrocodone. Dihydrocodeine is also a minor metabolite. Trace amounts of hydrocodone can also be found in the presence of approximately 100-fold higher concentrations of oxycodone or hydromorphine since it can be a pharmaceutical impurity in these medications. The presence of hydrocodone >100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphine is metabolized primarily in the liver and is excreted primarily as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6-hydroxy reduction metabolites. The presence of hydromorphone >100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection.
Hydromorphone is also a metabolite of hydrocodone; therefore, the presence of hydromorphone could also indicate exposure to hydrocodone. Dihydrocodeine is a semisynthetic narcotic analgesic prepared by the hydrogenation of codeine. It is also a minor metabolite of hydrocodone. It is metabolized to dihydromorphine and has a half-life of 3.4 to 4.5 hours. Oxycodone is metabolized to noroxycodone, oxymorphone, and their glucuronides and is excreted primarily via the kidney. The presence of oxycodone >100 ng/mL indicates exposure to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver to noroxymorphone and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and, therefore, the presence of oxymorphone could also indicate exposure to oxycodone.

**Useful For:** Detection and quantification of codeine, hydrocodone, oxycodone, morphine, hydromorphone, oxymorphone, noroxycodone, noroxymorphone, norhydrocodone, dihydrocodeine, and naloxone in urine. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

**Reference Values:**

Negative

Cutoff concentrations

**IMMUNOASSAY SCREEN**

300 ng/mL

Codeine by LC-MS/MS: 25 ng/mL
Dihydrocodeine by LC-MS/MS: 25 ng/mL
Hydrocodone by LC-MS/MS: 25 ng/mL
Norhydrocodone by LC-MS/MS: 25 ng/mL
Hydromorphone by LC-MS/MS: 25 ng/mL
Oxycodone by LC-MS/MS: 25 ng/mL
Noroxycodone by LC-MS/MS: 25 ng/mL
Oxymorphone by LC-MS/MS: 25 ng/mL
Noroxymorphone by LC-MS/MS: 25 ng/mL
Naloxone by LC-MS/MS: 25 ng/mL
Morphine by LC-MS/MS: 25 ng/mL

**Clinical References:**

urine during the first 24 hours. The ratio may fall below 1.0 after 24 hours, and after 30 hours, only morphine may be detected. Morphine is a naturally occurring narcotic analgesic obtained from the poppy plant, Papaver somniferum. Morphine is converted by hepatic metabolism to normorphine with a half-life of 2 to 4 hours. The presence of morphine in urine can indicate exposure to morphine, heroin, or codeine within 2 to 3 days. Ingestion of bakery products containing poppy seeds can also cause morphine to be excreted in urine. If excessively large amounts are consumed, this can result in urine morphine concentrations up to 2,000 ng/mL for a period of 6 to 12 hours after ingestion. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation, and 6-keto reduction to the 6-beta hydroxymetabolites. Hydromorphone and norhydrocodone are both metabolites of hydrocodone. Dihydrocodeine is also a minor metabolite. Trace amounts of hydrocodone can also be found in the presence of approximately 100-fold higher concentrations of oxycodone or hydromorphone since it can be a pharmaceutical impurity in these medications. The presence of hydrocodone >100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is metabolized primarily in the liver and is excreted primarily as the glucuronidated conjugate, with small amounts of parent drug and minor amounts of 6-hydroxy reduction metabolites. The presence of hydromorphone >100 ng/mL indicates exposure within 2 to 3 days prior to specimen collection. Hydromorphone is also a metabolite of hydrocodone; therefore, the presence of hydromorphone could also indicate exposure to hydrocodone. Dihydrocodeine is a semisynthetic narcotic analgesic prepared by the hydrogenation of codeine. It is also a minor metabolite of hydrocodone. It is metabolized to dihydromorphone and has a half-life of 3.4 to 4.5 hours. Oxycodone is metabolized to noroxycodone, oxymorphine, and their glucuronides, and is excreted primarily via the kidney. The presence of oxycodone >100 ng/mL indicates exposure to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver to noroxymorphone and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and, therefore, the presence of oxymorphone could also indicate exposure to oxycodone. Naloxone is a synthetic narcotic antagonist and used for partial or complete reversal of opioid depression induced by natural or synthetic opioids. It has also been incorporated into oral tablets of opioids to discourage abuse. The duration of action is dependent on the dose and route of administration. The half-life in adults is approximately 30 to 81 minutes. The detection interval for opiates is generally 2 to 3 days after last ingestion.

**Useful For:** Detection and quantification of codeine, hydrocodone, oxycodone, morphine, hydromorphone, oxymorphine, noroxycodone, noroxymorphone, norhydrocodone, dihydrocodeine, and naloxone in urine

**Interpretation:** This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

**Reference Values:**

Negative

Cutoff concentrations

Codeine by LC-MS/MS: 25 ng/mL
Dihydrocodeine by LC-MS/MS: 25 ng/mL
Hydrocodone by LC-MS/MS: 25 ng/mL
Norhydrocodone by LC-MS/MS: 25 ng/mL
Hydromorphone by LC-MS/MS: 25 ng/mL
Oxycodone by LC-MS/MS: 25 ng/mL
Noroxycodone by LC-MS/MS: 25 ng/mL
Oxymorphine by LC-MS/MS: 25 ng/mL
Noroxymorphine by LC-MS/MS: 25 ng/mL
Naloxone by LC-MS/MS: 25 ng/mL
Morphine by LC-MS/MS: 25 ng/mL

**Clinical References:**

Opiates, Serum or Plasma, Quantitative

**Interpretation:** Identification of specific drug(s) taken by specimen donor is problematic due to common metabolites, some of which are prescription drugs themselves. The absence of expected drug(s) and/or drug metabolite(s) may indicate non-compliance, inappropriate timing of specimen collection relative to drug administration, poor drug absorption, or limitations of testing. The concentration value must be greater than or equal to the cutoff to be reported as positive. A very small amount of an unexpected drug analyte in the presence of a large amount of an expected drug analyte may reflect pharmaceutical impurity. Interpretive questions should be directed to the laboratory.

**Reference Values:**
Drugs covered: codeine, morphine, 6-acetylmorphine, hydrocodone, hydromorphone, oxycodone, and oxymorphone. All drugs covered and the non-glucuronidated (free) form.

Positive cutoff: 2 ng/mL

For medical purposes only; not valid for forensic use.

Opioid Receptor, Mu 1 (OPRM1) Genotype for Naltrexone Efficacy, Blood

**Clinical Information:** The mu-opioid receptor (OPRM1) is the primary binding site of action for many opioid drugs and for binding of beta-endorphins. One of the effects of opiate and alcohol use is to increase release of beta-endorphins, which subsequently increases release of dopamine and stimulates cravings. Naltrexone is an opioid antagonist used to treat abuse of opiates, alcohol, and other substances. Naltrexone binds to OPRM1, preventing beta-endorphin binding and subsequently reducing the craving for substances of abuse. The A355G polymorphism (rs1799971) in exon 1 of the OPRM1 gene results in an amino acid change, Asn102Asp. Historically, this mutation has been referred to in the literature as 118A>G (Asn40Asp). The G allele leads to loss of the putative N-glycosylation site in the extracellular receptor region, causing a decrease in OPRM1 mRNA and protein levels, but a 3-fold increase in beta-endorphin binding at the receptor. Studies have shown individuals who carry at least 1 G allele have significantly better outcomes with naltrexone therapy including a lower rate of relapse (P=0.044), a longer time to return to heavy drinking, and a less than 20% relapse rate after 12 weeks of treatment compared with individuals who are homozygous for the A allele (55% relapse rate). Other studies indicated that 87.1% of G allele carriers had a good clinical outcome, compared with only 54.8% of individuals with the A/A genotype (odds ratio, 5.75; confidence interval, 1.88-17.54). A haplotype-based approach confirmed that the single OPRM1 355A->G locus was predictive of response to naltrexone treatment. However, other studies have called these findings into question. In addition, patients with the rs1799971 A/A genotype may have a decreased, but not absent, severity of intoxication and a decreased response when exposed to ethanol when compared to patients with the rs1799971 A/G and G/G genotypes. Furthermore, individuals with the rs1799971 A/A genotype may experience increased efficacy of opioids for pain and increased efficacy of opioid-related drugs to treat addiction. These individuals may also require a lower dose of opioids compared to patients with the rs1799971 A/G and G/G genotypes. Frequency of the 355G allele varies with ethnicity but ranges between 10% and 40% (European 20%, Asian 40%, African American 10%, and Hispanic 25%).

**Useful For:** Identifying individuals with a higher probability of successful treatment for alcoholism with naltrexone

**Interpretation:** An interpretative report will be provided.

**Reference Values:**
An interpretive report will be provided.


Opioid Receptor, Mu 1 (OPRM1) Genotype for Naltrexone Efficacy, Saliva

Clinical Information: The mu-opioid receptor (OPRM1) is the primary binding site of action for many opioid drugs and for binding of beta-endorphins. One of the effects of opiate and alcohol use is to increase release of beta-endorphins, which subsequently increases release of dopamine and stimulates cravings. Naltrexone is an opioid antagonist used to treat abuse of opiates, alcohol, and other substances. Naltrexone binds to OPRM1, preventing beta-endorphin binding and subsequently reducing the craving for substances of abuse. (1) The A355G polymorphism (rs1799971) in exon 1 of the OPRM1 gene results in an amino acid change, Asn102Asp. Historically, this mutation has been referred to in the literature as 118A>G (Asn40Asp). (2) The G allele leads to loss of the putative N-glycosylation site in the extracellular receptor region, causing a decrease in OPRM1 mRNA and protein levels, but a 3-fold increase in beta-endorphin binding at the receptor. (3) Studies have shown individuals who carry at least 1 G allele have significantly better outcomes with naltrexone therapy including a lower rate of relapse (P=0.044), a longer time to return to heavy drinking, and a less than 20% relapse rate after 12 weeks of treatment compared with individuals who are homozygous for the A allele (55% relapse rate). (4) Other studies indicated that 87.1% of G allele carriers had a good clinical outcome, compared with only 54.8% of individuals with the A/A genotype (odds ratio, 5.75; confidence interval, 1.88-17.54). (1) A haplotype-based approach confirmed that the single OPRM1 355A>G locus was predictive of response to naltrexone treatment. (1) However, other studies have called these findings into question. (5) In addition, patients with the rs1799971 A/A genotype may have a decreased, but not absent, severity of intoxication and a decreased response when exposed to ethanol when compared to patients with the rs1799971 A/G and G/G genotypes. (6) Furthermore, individuals with the rs1799971 A/A genotype may experience increased efficacy of opioids for pain and increased efficacy of opioid-related drugs to treat addiction. These individuals may also require a lower dose of opioids compared to patients with the rs1799971 A/G and G/G genotypes. (7) Frequency of the 355G allele varies with ethnicity but ranges between 10% and 40% (European 20%, Asian 40%, African American 10%, and Hispanic 25%).

Useful For: Identifying individuals with a higher probability of successful treatment for alcoholism with naltrexone. Genotyping patients who prefer not to have venipuncture done.

Interpretation: An interpretative report will be provided.

Reference Values: An interpretive report will be provided.


**FORNG**

**Orange IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**FORE**

**Orange Roughy IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal/Borderline 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 High Positive 4 5 6 17.50-49.99 50.0-99.99 >99.99 Very High Positive Very High Positive Very High Positive Very High Positive

**Reference Values:**

<0.35 kU/L

**ORNG**

**Orange, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
### Clinical References:

### Orchard Grass, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.
**Oregano IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Oregano, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>
Organic Acids Screen, Urine

Clinical Information: Organic acids occur as physiologic intermediates in a variety of metabolic pathways. Organic acidurias are a group of disorders in which one or more of these pathways are blocked, resulting in a deficiency of normal products and an abnormal accumulation of intermediate metabolites (organic acids) in the body. These excess metabolites are excreted in the urine. The incidence of individual inborn errors of organic acid metabolism varies from 1 in 10,000 to >1 in 1,000,000 live births. Collectively, their incidence approximates 1 in 3,000 live births. This estimate, however, does not include other inborn errors of metabolism (i.e., amino acid disorders, urea cycle disorders, congenital lactic acidemias) for which diagnosis and monitoring may also require organic acid analysis. All possible disease entities included, the incidence of conditions where informative organic acid profiles could be detected in urine is likely to approach 1 in 1,000 live births. Organic acidurias typically present with either an acute life-threatening illness in early infancy or unexplained developmental delay with intercurrent episodes of metabolic decompensations in later childhood. A situation of severe and persistent metabolic acidosis of unexplained origin, elevated anion gap, and severe neurologic manifestations, such as seizures, should be considered strong diagnostic indicators of one of these diseases. The presence of ketonuria, occasionally massive, provides an important clue toward the recognition of disorders, especially in the neonatal period. Hyperammonemia, hypoglycemia, and lactic acidemia are frequent findings, especially during acute episodes of metabolic decompensations.

Useful For: Diagnosis of inborn errors of metabolism

Interpretation: When no significant abnormalities are detected, the organic acid analysis is reported and interpreted in qualitative terms only. When abnormal results are detected, a detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional biochemical testing, and in vitro confirmatory studies (enzyme assay, molecular analysis).

Reference Values: An interpretive report will be provided.


Organism Referred for Identification, Aerobic Bacteria

Clinical Information: Organisms are referred to confirm identification or when the identity is unknown. This may provide helpful information regarding the significance of the organism, its role in the disease process, and its possible origin. Techniques employed may include conventional biochemical analysis, commercial identification strips or panels, MALDI-TOF mass spectrometry or sequencing nucleic acid of the 16S ribosomal RNA (rRNA) gene.

Useful For: Identification of pure isolates of aerobic bacteria

Interpretation: Genus and species are reported on aerobic bacterial isolates, whenever possible. Bacillus species will be reported out as "Large spore-forming aerobic gram-positive Bacillus, not
Bacillus cereus or Bacillus anthracis," unless species identification is specifically requested on the request form.

**Reference Values:**
Identification of organism


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**ANIDE 8114**

**Organism Referred for Identification, Anaerobic Bacteria**

**Clinical Information:** Anaerobic bacteria are the greatest component of the human body's normal bacterial flora colonizing the skin, oral cavity, and genitourinary and lower gastrointestinal tracts. Their presence is important in promoting vitamin and other nutrient absorption and in preventing infection with pathogenic bacteria. Anaerobes generally are of low pathogenicity, but may possess virulence factors such as endotoxin or polysaccharide capsules or produce extracellular toxins. Disease occurs when a large inoculum develops in an area lacking oxygen or with a poor blood supply. Typical anaerobic infections include peritonitis, abdominal or pelvic abscesses, endometritis, pelvic inflammatory disease, aspiration pneumonia, empyema, lung abscesses, sinusitis, brain abscesses, gas gangrene, and other soft tissue infections. Many Bacteroides produce beta-lactamase and are resistant to penicillins and cephalosporins. Imipenem, metronidazole, and clindamycin are effective agents, although resistance to clindamycin is increasing.

**Useful For:** Identification of anaerobic bacteria involved in human infections

**Interpretation:** Isolation of anaerobes in significant numbers from well-collected specimens from blood, other normally sterile body fluids, or closed collections of purulent fluid indicates infection with the identified organism.

**Reference Values:**
Identification of organism


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**FOPMU 75360**

**Organophosphate Pesticide Metabolites, Urine**

**Reference Values:**
Reporting limit determined each analysis.

- Creatinine (mg/L)
  - U.S. Population (10th - 90th percentiles, median)
    - All participants: 335 - 2370 mg/L, median: 1180 (n=22,245)
    - Males: 495 - 2540 mg/L, median: 1370 (n=10,610)
    - Females: 273 - 2170 mg/L, median 994 (n=11,635)

- Dimethylphosphate (DMP): None Detected ng/mL
Dimethylthiophosphate (DMTP): None Detected ng/mL

Dimethyldithiophosphate (DMDTP): None Detected ng/mL

Sum of Dimethyl Alkyl Phosphates (DMAP): None Detected nmol/L
CDC/NHANES 2007 - 2008 U.S. Population:
Generally less than 580 nmol/L

Sum of Dimethyl Alkyl Phosphates (DMAP) (Creatinine Corrected): None Detected nmol/g Creat
CDC/NHANES 2007 - 2008 U.S. Population:
Generally less than 550 nmol/g Creatinine

Diethylphosphate (DEP): None Detected ng/mL

Diethylthiophosphate (DETP): None Detected ng/mL

Diethyldithiophosphate (DEDTP): None Detected ng/mL

Sum of Diethyl Alkyl Phosphates (DEAP): None Detected nmol/L
CDC/NHANES 2007 - 2008 U.S. Population:
Generally less than 130 nmol/L

Sum of Diethyl Alkyl Phosphates (DEAP) (Creatinine Corrected): None Detected nmol/g Creat
CDC/NHANES 2007 - 2008 U.S. Population:
Generally less than 130 nmol/g Creatinine

Total Dialkyl Phosphates (DAP): None Detected nmol/L
CDC/NHANES 2007 - 2008 U.S. Population:
Generally less than 710 nmol/L

Total Dialkyl Phosphates (DAP) (Creatinine Corrected): None Detected nmol/g Creat
CDC/NHANES 2007 - 2008 U.S. Population:
Generally less than 680 nmol/g Creatinine

Specific Gravity Confirmation
Physiologic range: 1.010-0.030

**OROT**

**Orotic Acid, Urine**

**Clinical Information:** The urinary excretion of orotic acid, an intermediate in pyrimidine biosynthesis, is increased in many urea cycle disorders and in a number of other disorders involving the metabolism of arginine. The determination of orotic acid can be useful to distinguish between various causes of elevated ammonia (hyperammonemia). Hyperammonemia is characteristic of all urea cycle disorders, but orotic acid is elevated in only some, including ornithine transcarbamylase deficiency, citrullinemia, and argininosuccinic aciduria. Orotic acid is also elevated in the transport defects of dibasic amino acids (lysinuric protein intolerance and hyperornithinemia, hyperammonemia, and homocitrullinuria [HHH] syndrome), and greatly elevated in patients with hereditary orotic aciduria (uridine monophosphate synthase [UMPS] deficiency). Ornithine transcarbamylase (OTC) deficiency is
an X-linked urea cycle disorder that affects both males and due to random X-inactivation, females. It is thought to be the most common urea cycle disorder with an estimated incidence of 1:56,000. In OTC deficiency, carbamoyl phosphate accumulates and is alternatively metabolized to orotic acid. Allopurinol inhibits orotidine monophosphate decarboxylase and, when given to OTC carriers (who may have normal orotic acid excretion), can cause increased excretion of orotic acid. When orotic acid is measured after a protein load or administration of allopurinol, its excretion is a very sensitive indicator of ornithine transcarbamylase (OTC) activity. A carefully monitored allopurinol challenge followed by several determinations of a patient’s orotic acid excretion can be useful to identify OTC carriers, as approximately 20% of OTC mutations are not detectable by current molecular genetic testing methods.

**Useful For:** Evaluation of the differential diagnosis of hyperammonemia and hereditary orotic aciduria  
Sensitive indicator of ornithine transcarbamylase (OTC) activity after administration of allopurinol or a protein load to identify OTC carriers

**Interpretation:** The value for the orotic acid concentration is reported. The interpretation of the result must be correlated with clinical and other laboratory findings.

**Reference Values:**
- <2 weeks: 1.4-5.3 mmol/mol creatinine  
- 2 weeks-1 year: 1.0-3.2 mmol/mol creatinine  
- 2-10 years: 0.5-3.3 mmol/mol creatinine  
- > or =11 years: 0.4-1.2 mmol/mol creatinine

**Clinical References:**  

**FORRT**  
Orris Root (Iris florentina) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
- <0.35 kU/L

**OPTU**  
Orthostatic Protein, Timed Collection, Urine

**Clinical Information:** Orthostatic proteinuria refers to the development of increased proteinuria that develops only when the person is upright and resolves when recumbent or supine. This condition is usually seen in children, adolescents, or young adults, and accounts for the majority of cases of proteinuria in childhood. Orthostatic proteinuria usually does not indicate significant underlying renal pathology, and is usually not associated with other urine abnormalities such as hypoalbuminemia, hematuria, red blood cell casts, fatty casts, etc. Orthostatic proteinuria typically resolves over time. This test characterizes this condition by obtaining 2 urine collections within a 24-hour time frame, 1 collection obtained while the person is recumbent or supine, the other when upright.

**Useful For:** Diagnosis of orthostatic proteinuria As a second-order test for additional characterization of proteinuria of less than 3 grams/24 hours, particularly in children or adolescents
**Interpretation:** A supine 8-hour urine protein excretion of less than 68 mg/8 hours together with either 1) an elevated upright (16-hour) excretion of greater than 197 mg/16 hours, or 2) a 24-hour urine protein excretion of greater than 228 mg/24 hours is considered consistent with orthostatic proteinuria.

**Reference Values:**

Nighttime (supine) collection: <68 mg/8 hours
Reference values have not been established for patients <18 years of age.

Daytime collection: <197 mg/16 hours
Reference values have not been established for patients <18 years of age

**Clinical References:**


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**UOSMB**

**Osmolality, Body Fluid**

**Clinical Information:** Osmolality is a measure of dissolved solute particles in solution and is determined by the number, and not by the nature, of the particles in solution. Dissolved solutes change the physical properties of solutions, increasing the osmotic pressure and boiling point, and decreasing the vapor pressure and freezing point. Body fluids have the same osmolality as a corresponding serum sample taken at the same time. "True body fluids" include: ascitic, cerebrospinal, hydrocele, edema, pericardial, pleural, spermatocele and synovial fluids. Secretions not in equilibrium with the extracellular fluids of the body include gastric juice, saliva, and sweat.

**Useful For:** Determining the source and type of fluid

**Interpretation:** Not applicable

**Reference Values:**

No established reference values

**Clinical References:**

5. The Advance Osmometer Model 3250 User's guide

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**UOSMS**

**Osmolality, Serum**

**Clinical Information:** Osmolality is a measure of the number of dissolved solute particles in solution. It is determined by the number and not by the nature of the particles in solution. Dissolved solutes change the physical properties of solutions, increasing the osmotic pressure and boiling point and decreasing the vapor pressure and freezing point. The osmolality of serum increases with dehydration and decreases with overhydration. The patient receiving intravenous fluids should have a normal osmolality. If the osmolality rises, the fluids contain relatively more electrolytes than water. If the osmolality falls, relatively more water than electrolytes is being administered. Normally, the ratio of serum sodium, in mEq/L, to serum osmolality, in mOsm/kg, is between 0.43 and 0.5. The ratio may be distorted in drug intoxication. Generally, the same conditions that decrease or increase the serum
sodium concentration affect the osmolality. A comparison of measured and calculated serum osmolality produces a delta-osmolality. If this is >40 mOsm/kg a H2O in a critically ill patient, the prognosis is poor. An easy formula to calculate osmolality is: Osmolality (mOsm/kg H2O)=2 Na+ Glucose + BUN

**Useful For:** Evaluating acutely ill or comatose patients

**Interpretation:** An increased gap between measured and calculated osmolality may indicate ingestion of poison, ethylene glycol, methanol, or isopropanol.

**Reference Values:**
275-295 mOsm/kg

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.


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**Osmolality, Urine**

**Clinical Information:** Osmolality is an index of the solute concentration. Urine osmolality is a measure of the concentration of osmotically active particles, principally sodium, chloride, potassium, and urea; glucose can contribute significantly to the osmolality when present in substantial amounts in urine. Urinary osmolality corresponds to urine specific gravity in nondisease states. The ability of the kidney to maintain both tonicity and water balance of the extracellular fluid can be evaluated by measuring the osmolality of the urine either routinely or under artificial conditions. More information concerning the state of renal water handling or abnormalities of urine dilution or concentration can be obtained if urinary osmolality is compared to serum osmolality and if urine electrolyte studies are performed. Normally, the ratio of urine osmolality to serum osmolality is 1.0 to 3.0, reflecting a wide range of urine osmolality.

**Useful For:** Assessing the concentrating and diluting ability of the kidney

**Interpretation:** With normal fluid intake and normal diet, a patient will produce a urine of about 500 to 850 mosmol/kg water. Above age of 20 years there is an age dependent decline in the upper reference range of approximately 5 mOsm/kg/year. The normal kidney can concentrate a urine to 800 to 1,400 mosmol/kg and with excess fluid intake, a minimal osmolality of 40 to 80 mosmol/kg can be obtained. With dehydration, the urine osmolality should be 3 to 4 times the plasma osmolality.

**Reference Values:**
0-11 months: 50-750 mOsm/kg
> or =12 months: 150-1,150 mOsm/kg


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**Osmotic Fragility, Erythrocytes**

**Clinical Information:** Spherocytes are osmotically fragile cells that rupture more easily in a hypotonic solution than do normal RBCs. Because they have a low surface area:volume ratio, they lyse at a higher osmolarity than do normal discocyte (RBCs). Cells that have a larger surface area:volume ratio, such as target cells or hypochromic cells are more resistant to lysing. After incubation, an increase in hemolysis is seen in spherocytes. Hereditary spherocytosis typically has greater number of spherocytes than other causes of spherocytosis. Therefore, the degree of lysis is usually more pronounced, but this is not always the case. Some rare disorders can also cause marked fragility and hereditary spherocytosis cases can display moderate fragility.
Useful For: Evaluation of suspected hereditary spherocytosis associated hemolytic anemia
Confirming or detecting mild spherocytosis

Interpretation: An interpretive report will be provided.

Reference Values:
> or =12 months:
- 0.50 g/dL NaCl (unincubated): 3-53% hemolysis
- 0.60 g/dL NaCl (incubated): 14-74% hemolysis
- 0.65 g/dL NaCl (incubated): 4-40% hemolysis
- 0.75 g/dL NaCl (incubated): 1-11% hemolysis

Reference values have not been established for patients who are <12 months of age.


Osteocalcin, Serum

Clinical Information: Osteocalcin, the most important noncollagen protein in bone matrix, accounts for approximately 1% of the total protein in human bone. It is a 49-amino acid protein with a molecular weight of approximately 5800 daltons. Osteocalcin contains up to 3 gamma-carboxyglutamic acid residues as a result of posttranslational, vitamin K-dependent enzymatic carboxylation. Its production is dependent upon vitamin K and is stimulated by 1,25 dihydroxy vitamin D. Osteocalcin is produced by osteoblasts and is widely accepted as a marker of bone osteoblastic activity. Osteocalcin, incorporated into the bone matrix, is released into the circulation from the matrix during bone resorption and, hence, is considered a marker of bone turnover, rather than a specific marker of bone formation. Osteocalcin levels are increased in metabolic bone diseases with increased bone or osteoid formation including osteoporosis, osteomalacia, rickets, hyperparathyroidism, renal osteodystrophy, thyrotoxicosis, and in individuals with fractures, acromegaly, and bone metastasis. By means of osteocalcin measurements, it is possible to monitor therapy with antiresorptive agents (bisphosphonates or hormone replacement therapy [HRT]) in, for example, patients with osteoporosis or hyper-calcemia.(1) Decrease in osteocalcin is also observed in some disorders (eg, hypoparathyroidism, hypothyroidism, and growth hormone deficiency). Immunochemical and chromatographic studies have demonstrated considerable heterogeneity for concentrations of circulating osteocalcin in normal individuals and in patients with osteoporosis, chronic renal failure, and Pagetâ€™s disease. Both intact osteocalcin (amino acids 1-49) and the large N-terminal/midregion (N-MID) fragment (amino acids 1-43) are present in blood. Intact osteocalcin is unstable due to protease cleavage between amino acids 43 and 44. The N-MID-fragment, resulting from cleavage, is considerably more stable. This assay detects both the stable N-MID-fragment and intact osteocalcin.

Useful For: Monitoring and assessing effectiveness of antiresorptive therapy in patients treated for osteopenia, osteoporosis, Paget's disease, or other disorders in which osteocalcin levels are elevated As an adjunct in the diagnosis of medical conditions associated with increased bone turnover, including Paget's disease, cancer accompanied by bone metastases, primary hyperparathyroidism, and renal osteodystrophy

Interpretation: Elevated levels of osteocalcin indicate increased bone turnover. In patients taking antiresorptive agents (bisphosphonates or hormone replacement therapy), a decrease of > or =20% from baseline osteocalcin level (ie, prior to the start of therapy) after 3 to 6 months of therapy, suggests effective response to treatment.(2) Patients with diseases such as hyperparathyroidism, which can be cured, should have a return of osteocalcin levels to the reference range within 3 to 6 months after complete cure.(3)

Reference Values:
<18 years: not established
> or =18 years: 9-42 ng/mL

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### OAPNS 39855

**Ova and Parasite Examination, Non-Stool**

**Clinical Information:** A variety of different parasites may be found in respiratory specimens, liver cyst aspirates or abscesses, and tissues. These parasites may include protozoa (microscopic unicellular eukaryotes) and helminths (aka worms). Infection is often asymptomatic, but possible symptoms include diarrhea and malnutrition, intestinal obstruction, and rarely, death.

**Useful For:** Detection and identification of parasitic protozoa and the eggs and larvae of parasitic helminths

**Interpretation:** A positive result indicates the presence of the parasite but does not necessarily indicate that it is the cause of the patient’s symptoms. Some strains of protozoa are nonpathogenic and some helminths cause little or no illness.

**Reference Values:**

- Negative
- If positive, organism identified


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### OVAL 82826

**Ovalbumin, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

- Class IgE kU/L  Interpretation

FOVAS
57836
Ovarian Antibody Screen with Reflex to Titer, IFA
Reference Values:
Negative
Ovarian antibody screen is at 1:5 dilution

OVMU
82825
Ovomucoid, IgE
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  Page 1709

Ox-Eye Daisy, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

OXVM1

**OXA-48 and VIM, PCR (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

OXVRP

**OXA-48-like (blaOXA-48-like) and VIM (blaVIM) in Gram-Negative Bacilli, Molecular Detection, PCR**

**Clinical Information:** In the United States, Klebsiella pneumoniae carbapenemase (KPC) is the most common carbapenemase, followed by New Delhi metallo-beta-lactamase (NDM). OXA-48-like and VIM carbapenemases predominate in other parts of the globe, but do occur in the United States. The genes blaOXA-48-like and blaVIM encode OXA-48-like and VIM enzyme production, respectively. PCR is a sensitive, specific, and rapid means of identifying these genes. This test detects the genes encoding OXA-48-like (oxacillin-hydrolyzing beta-lactamase) and VIM (Verona integron-encoded metallo-beta-lactamase) types of beta-lactamases in bacterial isolates.

**Useful For:** Assessing pure isolates of Gram-negative bacilli for mechanism of carbapenem resistance

**Interpretation:** This PCR detects and differentiates blaOXA-48-like and blaVIM. A positive blaOXA-48-like (oxacillin-hydrolyzing beta-lactamase) PCR indicates that the isolate carries blaOXA-48-like. A positive VIM (Verona integron-encoded metallo-beta-lactamase) PCR indicates the isolate carries blaVIM. A negative result indicates the absence of detectable DNA.

**Reference Values:**
Not applicable

**Clinical References:**

OVSRP

**OXA-48-like (blaOXA-48-like) and VIM (blaVIM) Surveillance, PCR**

**Clinical Information:** In the United States, Klebsiella pneumoniae carbapenemase (KPC) is the most common carbapenemase, followed by New Delhi metallo-beta-lactamase (NDM). OXA-48-like and VIM carbapenemases predominate in other parts of the globe, but do occur in the United States. The genes blaOXA-48-like and blaVIM encode OXA-48-like and VIM enzyme production, respectively. PCR is a sensitive, specific, and rapid means of identifying these genes. This test detects the genes encoding OXA-48-like (oxacillin-hydrolyzing beta-lactamase) and VIM (Verona integron-encoded metallo-beta-lactamase) types of beta-lactamases in stool and perirectal/rectal/perianal/anal swabs. It can be used as a tool to find colonized patients. The Centers for Disease Control and Prevention recommends surveillance to detect unrecognized colonized patients who may be a potential source for transmission of carbapenemase-producing Gram-negative bacilli under certain circumstances. Such surveillance may be focused in certain high-risk settings or patient groups (eg, ICUs, long-term care facilities, patients transferred from areas or facilities with a high prevalence of the relevant type of resistance) or may be directed by infection prevention and control to investigate an outbreak.

**Useful For:** Identifying carriers of Gram-negative bacilli harboring OXA-48-like
Interpretation: This PCR assay detects and differentiates blaOXA-48-like and blaVIM in surveillance specimens (perirectal/rectal/perianal/anal swabs or stool). A positive OXA-48-like (oxacillin-hydrolyzing beta-lactamase) and/or VIM (Verona integron-encoded metallo-beta-lactamase) PCR indicates that the patient is colonized by a Gram-negative bacillus harboring blaOXA-48-like and/or blaVIM, respectively. A negative result indicates the absence of detectable DNA.

Reference Values: Not applicable


Oxalate Analysis in Hemodialysate

Clinical Information: Oxalate is a dicarboxylic acid, an end product of glyoxalate and glycerate metabolism that is excreted in the urine where it is a common component of kidney stones (up to 85%). Hyperoxaluria can be either genetic (eg, primary hyperoxaluria) or acquired/secondary (eg, enteric hyperoxaluria), and can lead to nephrocalcinosis and renal failure. Monitoring the adequacy of oxalate removal during hemodialysis can be useful in the management of patients with hyperoxaluria and renal failure, particularly following transplantation.

Useful For: Determining the amount of oxalate removed during a dialysis session Individualizing the dialysis prescription of hyperoxaluric patients

Interpretation: A steady decrease in oxalate signal is expected through dialysis procedure. Signals below 2 mcM should be considered ideal conditions. Total oxalate removed during a dialysis session can be estimated by multiplying the concentration of oxalate in the dialysate by the oxalate flow rate for each time period that the oxalate is measured.

Reference Values: Not applicable


Oxalate, 24 Hour, Urine

Clinical Information: Oxalate is an end product of glyoxalate and glycerate metabolism. Humans have no enzyme capable of degrading oxalate, so it must be eliminated by the kidney. In tubular fluid, oxalate can combine with calcium to form calcium oxalate stones. In addition, high concentrations of oxalate may be toxic for renal cells. Increased urinary oxalate excretion results from inherited enzyme deficiencies (primary hyperoxaluria), gastrointestinal disorders associated with fat malabsorption (secondary hyperoxaluria), or increased oral intake of oxalate-rich foods or vitamin C. Since increased
urinary oxalate excretion promotes calcium oxalate stone formation, various strategies are employed to lower oxalate excretion.

**Useful For:** Monitoring therapy for kidney stones Identifying increased urinary oxalate as a risk factor for stone formation Diagnosis of primary or secondary hyperoxaluria

**Interpretation:** An elevated urine oxalate (>0.46 mmol/24 hours) may suggest disease states such as secondary hyperoxaluria (fat malabsorption), primary hyperoxaluria (alanine glyoxalate transferase enzyme deficiency, glyceral dehydrogenase deficiency), idiopathic hyperoxaluria, or excess dietary oxalate or vitamin C intake. In stone-forming patients high urinary oxalate values, sometimes even in the upper limit of the normal range, are treated to reduce the risk of stone formation.

**Reference Values:**
0.11-0.46 mmol/24 hours
9.7-40.5 mg/24 hours

The reference value is for a 24-hour collection. Specimens collected for other than a 24-hour time period are reported in unit of mmol/L for which reference values are not established.


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**Oxalate, Pediatric, Random, Urine**

**Clinical Information:** Oxalate is an end product of glyoxalate and glycerate metabolism. Humans have no enzyme capable of degrading oxalate, so it must be eliminated by the kidney. In tubular fluid, oxalate can combine with calcium to form calcium oxalate stones. In addition, high concentrations of oxalate may be toxic for renal cells. Increased urinary oxalate excretion results from inherited enzyme deficiencies (primary hyperoxaluria), gastrointestinal disorders associated with fat malabsorption (secondary hyperoxaluria), or increased oral intake of oxalate-rich foods or vitamin C. Since increased urinary oxalate excretion promotes calcium oxalate stone formation, various strategies are employed to lower oxalate excretion.

**Useful For:** Monitoring therapy for kidney stones Identifying increased urinary oxalate as a risk factor for stone formation Diagnosis of primary or secondary hyperoxaluria A timed 24-hour urine collection is the preferred specimen for measuring and interpreting this urinary analyte. Random collections normalized to urinary creatinine may be of some clinical use in patients who cannot collect a 24-hour specimen, typically small children. Therefore, this random test is offered for children <16 years old.

**Interpretation:** An elevated urine oxalate (>0.46 mmol/day) may suggest disease states such as secondary hyperoxaluria (fat malabsorption), primary hyperoxaluria (alanine glyoxalate transferase enzyme deficiency, glyceral dehydrogenase deficiency), idiopathic hyperoxaluria, or excess dietary oxalate or vitamin C intake. In stone-forming patients high urinary oxalate values, sometimes even in the upper limit of the normal range, are treated to reduce the risk of stone formation. The urinary oxalate creatinine ratio varies widely in young children from <0.35 mmol/mL at birth to <0.15 mmol/mL at 1 year to <0.10 mmol/mL at 10 years and <0.05 mmol/mL at 20 years of age (see table below).(1) Oxalate/Creatinine (mg/mg) Age (year) 95th Percentile 0-0.5 <0.175 0.5-1 <0.139 1-2 <0.103 2-3 <0.08 3-5 <0.064 5-7 <0.056

**Reference Values:**
No established reference values

Oxalate, Plasma

Clinical Information: Oxalate is an insoluble dicarboxylic acid, which is an end product of liver metabolism of glyoxalate and glycerate. Humans lack an enzyme to degrade oxalate, and thus it must be eliminated by the kidney. Oxalate is a strong anion and tends to precipitate with calcium, especially in the urinary tract. Consequently, about 75% of all kidney stones contain calcium oxalate in some proportion. In renal failure oxalate is retained in the body and it can precipitate in tissues causing tissue toxicity, a condition called oxalosis. In the absence of disease, up to 90% of the body pool of oxalate is produced by hepatic metabolism and the other 10% is provided by oxalate contained in various foods. However, in the presence of gastrointestinal diseases that cause fat malabsorption the percentage absorbed from food can be much greater. The oxalate content of fruits and vegetables is quite variable, some being quite high and others virtually zero. Oxalate is freely filtered by the glomerulus. A smaller amount is also secreted in the proximal tubule. If the glomerular filtration rate (GFR) is decreased, oxalate begins to be retained in the body. However, in persons without primary hyperoxaluria (PH) or enteric hyperoxaluria (EH) plasma levels do not exceed the normal range until the GFR decreases below 10-20 mL/min/1.73 m(2). Plasma oxalate concentration is a reflection of the body pool size. When the pool increases, oxalate may precipitate in tissues and cause toxicity. Plasma oxalate pool size can be increased in various situations: Increased production and accumulation results from an abnormality in at least 3 different enzymes: Alanine glyoxalate transferase is necessary for the conversion of glyoxalate to alanine. A deficiency or intracellular mistargeting of this hepatic enzyme results in increased oxalate production (primary hyperoxaluria type 1). Glycolate reductase / hydroxypyruvate reductase deficiency in the liver and elsewhere in the body results in increased glyceralic acid formation, which leads to increased oxalate production (primary hyperoxaluria type 2). A third type of PH was recently shown to be due to mutations of HOGA1 that encodes the enzyme 4-hydroxy-2-oxoglutarate aldolase that is found in hepatic mitochondria (primary hyperoxaluria type 3). Increased oxalate load can be caused by increased absorption from the intestines after consuming large amounts of oxalate-rich foods such as rhubarb, spinach, or nuts. Certain abnormalities of the gastrointestinal tract can cause fat malabsorption including short bowel syndromes, inflammatory bowel disease, gastric bypass for obesity, and pancreatic insufficiency. All of these gastrointestinal abnormalities result in increased oxalate absorption from the intestinal tract. This is due to saponification of calcium by fatty acids in the colon, which in turn frees up oxalate anions for absorption. Decreased urinary oxalate excretion in chronic kidney disease (CKD) also caused oxalate retention in the body. Management of patients with PH and renal failure is difficult. Intensive dialyses are undertaken in an attempt to keep plasma levels below the level at which supersaturation and crystallization can occur in body tissues such as heart and bones (called oxalosis). PH is typically diagnosed by measuring oxalate levels in urine. However, as kidney function decreases, the renal excretion of oxalate also decreases. In such situations, plasma oxalate levels may be informative. Although plasma oxalate increases in CKD patients without PH, values are much higher in those CKD patients who do have PH. Plasma oxalate is often used to monitor these patients during critical periods in and around kidney transplantation, dialysis, or liver transplantation. Oxalate concentration in dialysate fluid is a reflection of the oxalate removed during dialysis.

Useful For: Assessing the body pool size of oxalate. The settings in which it has been most useful include patients with enzyme deficiencies, such as primary hyperoxaluria, which result in overproduction of oxalate or patients with enteric hyperoxaluria (EH). In the presence of chronic kidney disease (CKD), 3 uses of plasma oxalate are: - If primary hyperoxaluria (PH) is suspected in a patient with CKD of indeterminate cause, and urinary oxalate is not available, plasma oxalate can be used to aid in diagnosis. However although plasma oxalate levels are markedly elevated in PH patients with CKD suggesting the diagnosis, ancillary tests often are necessary to confirm it, such as genetic analysis of the 3 causative genes, or pathologic demonstration of oxalate crystals in tissues - Monitoring patients with renal failure and primary or enteric hyperoxaluria in order to be sure they are receiving enough dialysis - An aid in maintaining plasma oxalate levels below supersaturation (25-30 mcmol/L)

Interpretation: In nonacidified plasma specimens values near the reference range increase an average of 50% due to spontaneous oxalate generation. In patients with normal renal function, the presence of increased plasma oxalate concentration is good evidence for overproduction of oxalate (primary hyperoxaluria). In the presence of renal insufficiency, plasma oxalate levels are markedly elevated. Increased levels of plasma oxalate can be found in dialysis patients. In patients with possible primary...
hyperoxaluria and renal insufficiency, the diagnosis often can be made by knowing the plasma level of oxalate. However, ancillary tests, such as the demonstration of oxalate crystals in tissues (other than the kidney) or increased glycolate in dialysate (for patients on dialysis) often are necessary to make an accurate diagnosis.

Reference Values:
<1.6 mcmol/L

Reference values have not been established for patients under 21 and greater than 81 years of age.


Oxazepam (Serax), Serum
Reference Values:
Reference Range: 200 - 500 ng/mL

Oxcarbazepine Metabolite (MHC), Serum
Clinical Information: Oxcarbazepine (OCBZ) is approved as monotherapy and adjunctive therapy for partial seizures with and without secondary generalized seizures in adults and as adjunctive therapy for partial seizures in children. In humans, OCBZ is a prodrug that is almost immediately and completely metabolized to 10-hydroxy-10,11-dihydrocarbamazepine, known as monohydroxy carbamazepine (MHC), an active metabolite that is responsible for OCBZ's therapeutic effect. The elimination half-life is 1 to 2.5 hours for OCBZ and 8 to 10 hours for MHC. The therapeutic range (3â€“35 mcg/mL) is based on concentrations of the metabolite, not the parent drug; this assay measures the metabolite only. In clinical practice, the OCBZ dosage should be individually adjusted for each patient to achieve the desired therapeutic response. Toxicity associated with OCBZ includes hyponatremia, dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, and abnormal gait. These toxicities may be observed when blood concentrations are in the therapeutic range.

Useful For: Monitoring serum concentration during oxcarbazepine therapy Assessing compliance Assessing potential toxicity

Interpretation: Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next dose). Most individuals display optimal response to oxcarbazepine therapy when serum levels of the metabolite (measured in this assay) are between 3 and 35 mcg/mL. Some individuals may respond well outside of this range, or may display toxicity within the therapeutic range. Thus, interpretation should include clinical evaluation.

Reference Values:
Oxcarbazepine metabolite: 3-35 mcg/mL


Oxycodone - Free (Unconjugated), Serum
Reference Values:
Reporting Limit determined each analysis.
Oxycodone™ Free
Synonym(s): Roxicodone; OxyContin

Adult therapeutic range: 13 â€“ 120 ng/mL

Oxycodone Screen, Chain of Custody, Urine

Clinical Information: Opiates are the natural or synthetic drugs that have a morphine-like pharmacological action. Medically, opiates are used primarily for relief of pain. Opiates include morphine and drugs structurally similar to morphine (e.g., codeine, hydrocodone, hydromorphone, oxycodone, oxymorphone). Oxycodone is metabolized to noroxycodone, oxymorphone, and their glucuronides and is excreted primarily via the kidney. The presence of oxycodone greater than 100 ng/mL indicates exposure to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and therefore the presence of oxymorphone could also indicate exposure to oxycodone. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Useful For: Detection of oxycodone and oxymorphone in urine following chain-of-custody procedures. This chain-of-custody test is intended to be used in a setting where the test results can be used definitively to make a diagnosis.

Interpretation: A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (e.g., OXYCU / Oxycodone with Metabolite Confirmation, Urine) for more information. For information about drug testing, including estimated detection times, see Mayo Medical Laboratories Drugs of Abuse Testing Guide at http://www.mayomedicallaboratories.com/test-info/drug-book/index.html

Reference Values:
Negative
Screening cutoff concentration:
Oxycodone: 100 ng/mL


Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
**Useful For:** Detection of oxycodone and oxymorphone in urine

**Interpretation:** A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (eg, OXYCU / Oxycodone with Metabolite Confirmation, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at [http://www.mayomedicallaboratories.com/test-info/drug-book/index.html](http://www.mayomedicallaboratories.com/test-info/drug-book/index.html)

**Reference Values:**
Negative
  Screening cutoff concentration:

  Oxycodone: 100 ng/mL


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**OXYCX**

**Oxycodone with Metabolite Confirmation, Chain of Custody, Urine**

**Clinical Information:** Oxycodone is metabolized to noroxycodone, oxymorphone, and their glucuronides and is excreted primarily via the kidney. The presence of oxycodone >100 ng/mL indicates exposure to oxycodone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver to noroxymorphone and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and, therefore, the presence of oxymorphone could also indicate exposure to oxycodone. The detection interval for opiates is generally 2 to 3 days after last ingestion. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection and quantification of oxycodone, oxymorphone, noroxycodone, and noroxymorphonein urine Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

**Reference Values:**
Negative
  Cutoff concentrations:

  Oxycodone Immunoassay screen: 100 ng/mL
  Oxycodone-by LC-MS/MS: 25 ng/mL
  Noroxycodone-by LC-MS/MS: 25 ng/mL
  Oxymorphone-by LC-MS/MS: 25 ng/mL
  Noroxymorphone-by LC-MS/MS: 25 ng/mL

Oxycodeone with Metabolite Confirmation, Urine

Clinical Information: Oxycodeone is metabolized to noroxycodone, oxymorphone, and their glucuronides and is excreted primarily via the kidney. The presence of oxycodeone >100 ng/mL indicates exposure to oxycodeone within 2 to 3 days prior to specimen collection. Oxymorphone is metabolized in the liver to noroxymorphone and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodeone and, therefore, the presence of oxymorphone could also indicate exposure to oxycodeone. The detection interval for opiates is generally 2 to 3 days after last ingestion.

Useful For: Detection and quantification of oxycodeone, oxymorphone, noroxycodone, and noroxymorphone in urine

Interpretation: This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

Reference Values:

Negative
Cutoff concentrations:
Oxycodeone-by LC-MS/MS: 25 ng/mL
Noroxycodone-by LC-MS/MS: 25 ng/mL
Oxymorphone-by LC-MS/MS: 25 ng/mL
Noroxymorphone-by LC-MS/MS: 25 ng/mL

Clinical References:

Oxygen Dissociation, P50, Erythrocytes

Clinical Information: Abnormal oxygen affinity is demonstrated in the presence of some hemoglobin variants: -High oxygen affinity causes erythrocytosis -Low oxygen affinity causes cyanosis and/or low oxygen saturation. Increased oxygen affinity of hemoglobin, reflected in a low p50, left-shifted oxygen dissociation curve, and loss of normal sigmoidal configuration, are characteristic of many hemoglobin variants that are responsible for polycythemia. Measurement of oxygen affinity is an important method for diagnosis of these disorders.

Useful For: Identifying hemoglobin variants associated with polycythemia or cyanotic and hypoxic disorders

Interpretation: Normal: p50 =24 to 30 mm Hg (with sigmoidal oxygen dissociation curve) An interpretive report will be provided

Reference Values:
> or =12 months: 24-30 mm Hg
Reference values have not been established for patients who are <12 months of age.

OXYMU

**Oxymorphone Confirmation, Urine**

**Clinical Information:** Oxymorphone is metabolized in the liver to noroxymorphone and excreted via the kidney primarily as the glucuronide conjugates. Oxymorphone is also a metabolite of oxycodone and, therefore, the presence of oxymorphone could also indicate exposure to oxycodone. The detection interval for opiates is generally 2 to 3 days after last ingestion.

**Useful For:** Detection and quantification of oxymorphone and noroxymorphone in urine

**Interpretation:** This procedure reports the total urine concentration; this is the sum of the unconjugated and conjugated forms of the parent drug.

**Reference Values:**

Negative

Cutoff concentrations:

- Oxymorphone-by LC-MS/MS: 25 ng/mL
- Noroxymorphone-by LC-MS/MS: 25 ng/mL

**Clinical References:**


OXYBS

**Oxysterols, Blood Spots**

**Clinical Information:** Niemann-Pick disease types A, B, and C are a group of autosomal recessive lysosomal storage disorders affecting metabolism of specific lipids within cells. Niemann-Pick types A and B (NPA and NPB), (1,2) are caused by a deficiency of sphingomyelinase resulting in extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and, to a lesser degree, brain. Classification of NPA or NPB is based on the age of onset as well as the severity of symptoms. NPA disease is more severe and characterized by early onset with feeding problems, hepatosplenomegaly, cherry red maculae, developmental arrest and deterioration, hypotonia, and interstitial lung disease. Individuals with NPA typically die by age 3. NPB disease is characterized by later onset and milder symptoms with survival into adulthood. Some patients have been described with intermediary phenotypes. Characteristic of the disease are large lipid-laden foam cells on bone marrow biopsy. The combined prevalence of NPA and NPB is estimated to be 1 in 250,000. NPA and NPB are inherited in an autosomal recessive manner and are caused by mutations in the SMPD1 gene. Although there is a higher frequency of type A among the Ashkenazi Jewish population, both types are pan-ethnic. Individuals with NPD types A and B typically have elevation of the oxysterol lyso-sphingomyelin (LSM); cholestane-3 beta, 5 alpha, 6 beta-triol (COT), and/or 7-ketocholesterol (7-KC) may also be elevated. Molecular genetic testing for NPA and NPB disease is also available (see NPABZ / Niemann-Pick Disease, Types A and B, Full Gene Analysis). Niemann-Pick disease type C (NPC), is caused by a defect in cellular cholesterol trafficking resulting in the accumulation of unesterified cholesterol in late endosomes/lysosomes.(3) Age of onset is variable and ranges from the perinatal period to adulthood, and clinical presentation is also highly variable. Most individuals are diagnosed during childhood with symptoms including ataxia, vertical supranuclear gaze palsy, dystonia, progressive speech deterioration, and seizures resulting in death by the second or third decade of life. Infants may present with fetal ascites or neonatal liver disease with prolonged jaundice, hepatosplenomegaly, and respiratory failure. Those without liver and pulmonary disease may present with hypotonia and developmental delay. Adult-onset NPC is associated with a slower progression and is characterized by psychiatric illness, ataxia, dystonia, and speech difficulties. The incidence of NPC is approximately 1 in 120,000-150,000 live births. NPC is an autosomal recessive condition and is caused by mutations in either the NPC1 or NPC2 genes. Individuals with NPC exhibit elevated levels of oxysterol cholestane-3 beta, 5 alpha, 6 beta-triol (COT); 7-ketocholesterol (7-KC) may also be elevated. For molecular confirmation, genetic testing for NPC disease can be performed (see NPCZ / Niemann-Pick Type C Disease, Full Gene Analysis).
Useful For: Investigation of possible diagnoses of Niemann-Pick disease type C (NPC) and types A or B (NPA or NPB) in blood spot specimens Monitoring of individuals with NPC disease

Interpretation: An elevation of cholestane-3 beta, 5 alpha, 6 beta-triol (COT) is highly suggestive of Niemann-Pick disease type C disease. An elevation of lyso-sphingomyelin (LSM) is highly suggestive of Niemann-Pick disease type A or B disease.

Reference Values:

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestane-3beta, 5alpha, 6beta-triol</td>
<td>&lt; or =0.800 nmol/mL</td>
</tr>
<tr>
<td>Lyso-sphingomyelin</td>
<td>&lt; or =0.100 nmol/mL</td>
</tr>
</tbody>
</table>


Oxysterols, Plasma

Clinical Information: Niemann-Pick disease types A, B, and C are a group of autosomal recessive lysosomal storage disorders affecting metabolism of specific lipids within cells. Niemann-Pick types A and B (NPA and NPB), (1,2) are caused by a deficiency of sphingomyelinase resulting in extensive storage of sphingomyelin and cholesterol in the liver, spleen, lungs, and, to a lesser degree, brain. Classification of NPA or NPB is based on age of onset as well as the severity of symptoms. NPA disease is more severe and characterized by early onset with feeding problems, hepatosplenomegaly, cherry red maculae, developmental arrest and deterioration, hypotonia, and interstitial lung disease. Individuals with NPA typically die by age 3. NPB disease is characterized by later onset and milder symptoms with survival into adulthood. Some patients have been described with intermediary phenotypes. Characteristic of the disease are large lipid-laden foam cells on bone marrow biopsy. The combined prevalence of NPA and NPB is estimated to be 1 in 250,000. NPA and NPB are inherited in an autosomal recessive manner and are caused by mutations in the SMPD1 gene. Although there is a higher frequency of type A among the Ashkenazi Jewish population, both types are pan-ethnic. Individuals with NPD types A and B typically have elevation of the oxysterol lyso-sphingomyelin (LSM); cholestane-3 beta, 5 alpha, 6 beta-triol and/or 7-ketocholesterol (7-KC) may also be elevated. Molecular genetic testing for NPA and NPB disease is also available (see NPABZ / Niemann-Pick Disease, Types A and B, Full Gene Analysis). Niemann-Pick disease is caused by mutations of the gene encoding the enzyme acid sphingomyelinase (ASM), which catalyzes the conversion of sphingomyelin to ceramide and choline. The accumulation of sphingomyelin within the lysosomes of liver, spleen, and lungs results in organ dysfunction and cell death. The clinical manifestations of Niemann-Pick disease include feeding difficulties, hepatosplenomegaly, respiratory distress, and developmental delays. The disease is progressive and typically results in death by the age of 3 years.
disease type C (NPC) is caused by a defect in cellular cholesterol trafficking resulting in the accumulation of unesterified cholesterol in late endosomes/lysosomes. (3) Age of onset is variable and ranges from the perinatal period to adulthood, and clinical presentation is also highly variable. Most individuals are diagnosed during childhood with symptoms including ataxia, vertical supranuclear gaze palsy, dystonia, progressive speech deterioration, and seizures resulting in death by the second or third decade of life. Infants may present with fetal ascites or neonatal liver disease with prolonged jaundice, hepatosplenomegaly, and respiratory failure. Those without liver and pulmonary disease may present with hypotonia and developmental delay. Adult-onset NPC is associated with a slower progression and is characterized by psychiatric illness, ataxia, dystonia, and speech difficulties. The incidence of NPC is approximately 1 in 120,000 to 150,000 live births. NPC is an autosomal recessive condition and is caused by mutations in either the NPC1 or NPC2 genes. Individuals with NPC exhibit elevated levels of oxysterol cholestane-3 beta,5 alpha,6 beta-triol (COT); 7-ketocholesterol (7-KC) may also be elevated. For molecular confirmation, genetic testing for NPC disease can be performed (see NPCZ / Niemann-Pick Type C Disease, Full Gene Analysis).

Useful For: Investigation of possible diagnoses of Niemann-Pick disease type C (NPC) and types A or B (NPA or NPB) in plasma specimens Monitoring of individuals with Niemann-Pick type C disease

Interpretation: An elevation of cholestane-3 beta, 5 alpha, 6 beta-triol (COT) is highly suggestive of Niemann-Pick disease type C (NPC). An elevation of lyso-sphingomyelin (LSM) is highly suggestive of Niemann-Pick type A or B (NPA or NPB) disease.

Reference Values:
CHOLESTANE-3BETA, 5ALPHA, 5BETA-TRIOL
Cutoff: < or =0.02 nmol/mL

7-KETOCHOLESTEROL
Cutoff: < or =0.05 nmol/mL

LYSO-SPHINGOMYELIN
Cutoff: < or =0.02 nmol/mL

**Oyster, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


**P0 (Pzero) Antibodies**

**Interpretation:** Antibodies against P0 protein occur in 46% of patients with Meniere’s disease, 40% of patients with otosclerosis, 28% of patients with idiopathic progressive sensorineural hearing loss and 18% of patients with sudden deafness and in 4% of control subjects (Tomasi JP, Lona A, Deggouj N, Gersdorff M. Autoimmune sensorineural hearing loss in young patients: an exploratory study. Laryngoscope, 2001;111:2050-3v)

**Reference Values:** Qualitative Test â€“ Positive or Negative

**p16 (INK4a/CDKN2A) Immunostain, Technical Component Only**
**Clinical Information:** p16 (INK4a/CDKN2A) is a cell cycle regulatory protein that is overexpressed in cervical dysplasia related to human papilloma virus (HPV) infection. Nuclear and cytoplasmic staining is seen in dysplastic squamous cervical epithelial cells infected with HPV, but not in normal cells. A subset of pancreatic islet cells and dendritic cells show expression of p16, and can serve as positive control.

**Useful For:** Aids in the identification of human papilloma virus infection

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
2. Doxtader EE, Katzenstein AL: The relationship between p16 expression and high-risk human papillomavirus infection in squamous cell carcinomas from sites other than uterine cervix: a study of 137 cases. Human Pathol 2012;43:327-332

**P40NA 70526**

**p40 + Napsin A Immunostain, Technical Component Only**

**Clinical Information:** p40 is an antibody (detected by the chromogen 3,3′-diaminobenzidine [DAB]) that recognizes the deltaNp63 isoform of p63. This isoform may exert an oncogenic effect and is selectively expressed in squamous cell carcinoma. Napsin A is an aspartic proteinase involved in the proteolytic processing of surfactant precursors in the normal alveolar epithelium. In normal tissues, napsin A is expressed in the cytoplasm of alveolar macrophages, type II pneumocytes, pancreatic ducts and acini, and in renal tubules (detected by the chromogen fast red). Napsin A has clinical utility for the identification of primary lung adenocarcinomas. Napsin A is also positive in a subset of thyroid and renal cell carcinomas (especially papillary types).

**Useful For:** p40 aids in the classification of carcinomas and lymphomas Napsin A aids in the identification of primary lung adenocarcinoma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**P40 70527**

**p40 Immunostain, Technical Component Only**

**Clinical Information:** p40 is an antibody that recognizes the deltaNp63 isoform of p63. This isoform may exert an oncogenic effect and is selectively expressed in squamous cell carcinoma.

**Useful For:** Diagnosis and classification of carcinomas and lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**P53 70528**

**p53 Immunostain, Technical Component Only**

**Clinical Information:** p53 is a tumor-suppressor protein. Genetic events (mutation and deletion) that affect both P53 alleles can lead to loss of cell cycle control in the setting of DNA damage, resulting in genetic instability and neoplastic transformation. Mutated p53 also has a prolonged half-life compared to wild-type p53 and, thus, accumulates in the nucleus and can be detected by immunohistochemistry. Abnormalities of the P53 gene are one of the most common genetic changes associated with cancer and can be found in a wide variety of tumor types, where they are generally associated with a worse prognosis. The p53 protein can be readily detected in a subset of cancers of the colon, stomach, bladder, breast, lung, and testes and in melanoma and lymphoma.

**Useful For:** Aids in the identification of neoplastic cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation
for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**P57**

**70529**

**p57 (KIP2/CDKN1C) Immunostain, Technical Component Only**

**Clinical Information:**
P57 (KIP2/CDKN1C) is a cell cycle regulatory protein that acts as a tumor-suppressor gene by inhibiting the activity of cyclin dependent kinases. P57 is expressed in the cytotrophoblasts, intermediate trophoblasts, and villous stromal cells in normal placenta. Loss of p57 expression is associated with complete hydatidaform moles, and can help distinguish them from partial hydatidiform moles and hydropic abortions.

**Useful For:** Aids in the identification of cytotrophoblasts, intermediate trophoblasts, and villous stromal cells.

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**P62**

**70629**

**p62 Immunostain, Technical Component Only**

**Clinical Information:** Argyrophilic grain disease (AGD) is a common, late-onset dementia characterized by the presence of argyrophilic grains and coiled bodies. AGD is a frequent pathologic finding in patients who have been diagnosed with amnestic-type mild cognitive impairment. Immunohistochemical detection of ubiquitin-binding protein p62 is a sensitive and reproducible method
to identify grain pathology in AGD.

**Useful For:** Aids in diagnosing argyrophilic grain disease

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**P63 Immunostain, Technical Component Only**

**Clinical Information:** The p63 protein is a member of the p53 family of tumor-suppressor proteins. The predominant localization of p63 protein is in the basal layer of stratified squamous and transitional epithelia. p63 is negative in malignant tumors of the prostate. Striated muscle staining may be observed with p63.

**Useful For:** Aids in identifying squamous, urothelial, or myoepithelial differentiation in tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**Pacific Squid, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE...
antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<tr>
<th>Class</th>
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<tr>
<td>0</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**PDSOX 62738**

**Pain Clinic Drug Screen, Chain of Custody, Urine**

**Clinical Information:** This panel was designed to screen for and confirm by gas chromatography-mass spectrometry (GC-MS) or gas chromatography-flame ionization detection (GC-FID) the following drugs: -Barbiturates -Benzodiazepines -Cocaine -Ethanol -Methadone -Phencyclidine -Tetrahydrocannabinol Confirmation by liquid chromatograph-tandem mass spectrometry (LC-MS/MS) is completed for all opiates and amphetamines. This panel uses the screening technique that involves immunoassay testing for drugs by class. All positive screening results are confirmed by GC-MS, GC-FID, or LC-MS/MS, and quantitated, before a positive result is reported. The panel includes PDSUX / Drug Screen, Prescription/OTC, Chain of Custody, Urine, which looks for a broad spectrum of prescription and over-the-counter drugs. It is designed to detect drugs that have toxic effects, as well as known antidotes or active therapies that a clinician can initiate to treat the toxic effect. The test is intended to help physicians manage an apparent overdose or intoxicated patient, to determine if a specific set of symptoms might be due to the presence of drugs, or to evaluate a patient who might be abusing these drugs intermittently. The test is not designed to screen for intermittent use of illicit drugs. Chain-of-custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.
Useful For: Detecting drug abuse involving amphetamines, barbiturates, benzodiazepines, cocaine, ethanol, methadone, opiates, phencyclidine, and tetrahydrocannabinol. Detection and identification of prescription or over-the-counter drugs frequently found in drug overdose or used with a suicidal intent. This test is intended to be used in a setting where the identification of the drug is required. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

Interpretation: A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (e.g., AMPHX / Amphetamines Confirmation, Chain of Custody, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at http://www.mayomedicallaboratories.com/test-info/drug-book/index.html

Reference Values:
Negative

Screening cutoff concentrations
Amphetamines: 500 ng/mL
Barbiturates: 200 ng/mL
Benzodiazepines: 100 ng/mL
Cocaine (benzoylcegonine-cocaine metabolite): 150 ng/mL
Ethanol: 10 mg/dL
Methadone metabolite: 300 ng/mL
Opiates: 300 ng/mL
Phencyclidine: 25 ng/mL
Tetrahydrocannabinol carboxylic acid: 50 ng/mL

This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.

Clinical References:

Pain Clinic Drug Screen, Urine

Clinical Information: This panel was designed to screen for and confirm by gas chromatography-mass spectrometry (GC-MS) or gas chromatography-flame ionization detection (GC-FID) the following drugs: -Barbiturates -Benzodiazepines -Cocaine -Ethanol -Methadone -Phencyclidine -Tetrahydrocannabinol Confirmation by liquid chromatograph-tandem mass spectrometry (LC-MS/MS) is completed for all opiates and amphetamines. This panel uses the screening technique which involves immunoassay testing for drugs by class. All positive screening results are confirmed by GC-MS, GC-FID, or LC-MS/MS, and quantitated, before a positive result is reported. The panel includes PDSU / Drug Screen, Prescription/OTC, Urine, which looks for a broad spectrum of prescription and over-the-counter drugs. It is designed to detect drugs that have toxic effects, as well as known antidotes or active therapies that a clinician can initiate to treat the toxic effect. The test is intended to help physicians manage an apparent overdose or intoxicated patient, to determine if a specific set of symptoms might be due to the presence of drugs, or to evaluate a patient who might be abusing these drugs intermittently. The test is not designed to screen for intermittent use of illicit drugs.

Useful For: Detecting drug abuse involving amphetamines, barbiturates, benzodiazepines, cocaine, ethanol, methadone, opiates, phencyclidine, and tetrahydrocannabinol. Detection and identification of prescription or over-the-counter drugs frequently found in drug overdose or used with a suicidal intent.
This test is intended to be used in a setting where the identification of the drug is required.

**Interpretation:** A positive result indicates that the patient has used the drugs detected in the recent past. See individual tests (eg, AMPHU / Amphetamines Confirmation, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at http://www.mayomedicallaboratories.com/test-info/drug-book/index.html

**Reference Values:**

Negative

Screening cutoff concentrations:

- Amphetamines: 500 ng/mL
- Barbiturates: 200 ng/mL
- Benzodiazepines: 100 ng/mL
- Cocaine (benzoylecgonine-cocaine metabolite): 150 ng/mL
- Ethanol: 10 mg/dL
- Methadone metabolite: 300 ng/mL
- Opiates: 300 ng/mL
- Phencyclidine: 25 ng/mL
- Tetrahydrocannabinol carboxylic acid: 50 ng/mL

This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.

**Clinical References:**


**PNRCH**

65061  Pain Clinic Immunoassay Panel, Urine

**Reference Values:**

Only orderable as part of a profile. For more information see PNCSU / Pain Clinic Survey, Urine.

**PN10X**

62911  Pain Clinic Survey 10, Chain of Custody

**Reference Values:**

Only orderable as part of a profile. For more information see PANOX / Pain Clinic Survey 10, Chain of Custody, Urine.

**PANOX**

62737  Pain Clinic Survey 10, Chain of Custody, Urine

**Clinical Information:**

This assay was designed to test for and confirm by gas chromatography-mass spectrometry (GC-MS) the following: -Barbiturates -Benzodiazepines -Cocaine -Methadone -Phencyclidine -Tetrahydrocannabinol

Confirmation by liquid chromatograph-tandem mass spectrometry (LC-MS/MS) is completed for all opiates and amphetamines. This test uses the simple screening technique which involves immunologic testing for drugs by class. Oxycodone is not detected well with the opiate screening assay; therefore, OPATX / Opiate Confirmation, Chain of Custody, Urine is included to detect this drug. All positive screening results are confirmed by GC-MS or LC-MS/MS, and quantitated, before a positive result is reported. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times;
this control implies that the opportunity for specimen tampering would be limited.

**Useful For:** Detecting drug use involving amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, and tetrahydrocannabinol. This chain-of-custody test is intended to be used in a setting where the test results can be used to make a definitive diagnosis.

**Interpretation:** A positive result derived by this testing indicates that the patient has used 1 of the drugs detected by this technique in the recent past. See individual tests (e.g., AMPHX / Amphetamines Confirmation, Chain of Custody, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at [http://www.mayomedicallaboratories.com/test-info/drug-book/index.html](http://www.mayomedicallaboratories.com/test-info/drug-book/index.html)

**Reference Values:**

- Negative
- Screening cutoff concentrations
  - Amphetamines: 500 ng/mL
  - Barbiturates: 200 ng/mL
  - Benzodiazepines: 100 ng/mL
  - Cocaine (benzoylecgonine-cocaine metabolite): 150 ng/mL
  - Methadone metabolite: 300 ng/mL
  - Opiates: 300 ng/mL
  - Phencyclidine: 25 ng/mL
  - Tetrahydrocannabinol carboxylic acid: 50 ng/mL

This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.

**Clinical References:**

**Pain Clinic Survey, Urine**

**Clinical Information:** This test uses the simple screening technique that involves immunologic testing for drugs by class. All positive immunoassay screening results are confirmed by gas chromatography-mass spectrometry (GC-MS) or liquid chromatography-tandem mass spectrometry (LC-MS/MS), and quantitated, before a positive result is reported. This assay was designed to test for and confirm by the following: -Barbiturates -Benzodiazepines -Cocaine -Phencyclidine -Tetrahydrocannabinol Confirmation by LC-MS/MS is completed for all amphetamines. The targeted opioid screen portion is performed by liquid chromatography-tandem mass spectrometry, high-resolution accurate mass (LC-MS/MS HRAM) and is completed for all opioids. Opioids are a large class of medications commonly used to relieve acute and chronic pain or help manage opioid abuse and dependence. Medications that fall into this class include: buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, tapentadol, tramadol, and others. Opioids work by binding to the opioid receptors that are found in the brain, spinal cord, gastrointestinal tract, and other organs. Common side effects include drowsiness, confusion, nausea, constipation, and in severe cases respiratory depression depending on the dose. These medications can also produce physical and psychological dependence and have a high risk for abuse and diversion, which is one of the main reasons many professional practice guidelines recommend compliance testing in patients prescribed these medications. Opioids are readily absorbed from the gastrointestinal tract, nasal mucosa, lungs, and after subcutaneous or intramuscular injection. Opioids are primarily excreted from the kidney in both free and conjugated forms. This assay does not hydrolyze the urine sample and looks for both parent drugs and metabolites (including glucuronide forms). The detection window for most opioids in urine is approximately 1 to 3 days with longer detection times for some compounds (i.e., methadone).

**Useful For:** Detecting drug use involving amphetamines, barbiturates, benzodiazepines, cocaine, opioids, phencyclidine, and tetrahydrocannabinol. This test is intended to be used in a setting where the
test results can be used to make a definitive diagnosis.

**Interpretation:** A positive result derived by this testing indicates that the patient has used 1 of the drugs detected by these techniques in the recent past. See individual tests (eg, AMPHU / Amphetamines Confirmation, Urine) for more information. For information about drug testing, including estimated detection times, see Drugs of Abuse Testing at http://www.mayomedicallaboratories.com/test-info/drug-book/index.html

**Reference Values:**

**ADULT:**

- Normal
- Cutoff concentrations
  - Oxidants: 200 mg/L
  - Nitrites: 500 mg/L

**PNRCH:**

- Negative
- Screening cutoff concentrations:
  - Amphetamines: 500 ng/mL
  - Barbiturates: 200 ng/mL
  - Benzodiazepines: 100 ng/mL
  - Cocaine (benzylecgonine-cocaine metabolite): 150 ng/mL
  - Phencyclidine: 25 ng/mL
  - Tetrahydrocannabinol carboxylic acid: 50 ng/mL

  This report is intended for use in clinical monitoring or management of patients. It is not intended for use in employment-related testing.

**TOPSU:**

- Not Detected

- Cutoff concentrations:
  - Codeine: 25 ng/mL
  - Codeine-6-beta-glucuronide: 100 ng/mL
  - Morphine: 25 ng/mL
  - Morphine-6-beta-glucuronide: 100 ng/mL
  - 6-monoacetylmorphine: 25 ng/mL
  - Hydrocodone: 25 ng/mL
  - Norhydrocodone: 25 ng/mL
  - Dihydrocodeine: 25 ng/mL
  - Hydromorphone: 25 ng/mL
  - Hydromorphone-3-beta-glucuronide: 100 ng/mL
  - Oxycodone: 25 ng/mL
  - Noroxycodone: 25 ng/mL
  - Oxymorphone: 25 ng/mL
  - Oxymorphone-3-beta-glucuronide: 100 ng/mL
  - Noroxymorphone: 25 ng/mL
  - Fentanyl: 2 ng/mL
  - Norfentanyl: 2 ng/mL
  - Meperidine: 25 ng/mL
  - Normeperidine: 25 ng/mL
  - Naloxone: 25 ng/mL
  - Naloxone-3-beta-glucuronide: 100 ng/mL
  - Methadone: 25 ng/mL
  - EDDP: 25 ng/mL
  - Propoxyphene: 25 ng/mL
  - Norpropoxyphene: 25 ng/mL
  - Tramadol: 25 ng/mL
  - O-desmethyltramadol: 25 ng/mL
Tapentadol: 25 ng/mL
N-desmethyltapentadol: 50 ng/mL
Tapentadol-beta-glucuronide: 100 ng/mL
Buprenorphine: 5 ng/mL
Norbuprenorphine: 5 ng/mL
Norbuprenorphine glucuronide: 20 ng/mL


<table>
<thead>
<tr>
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<tbody>
<tr>
<td>57129</td>
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<tr>
<td></td>
<td>0-88 pg/mL</td>
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</table>

<table>
<thead>
<tr>
<th>FPAN1</th>
<th>Pancreatic Elastase-1</th>
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<tr>
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</tr>
<tr>
<td></td>
<td>Normal: &gt;200 mcg/g</td>
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<tr>
<td></td>
<td>Moderate Pancreatic Insufficiency: 100-200 mcg/g</td>
</tr>
<tr>
<td></td>
<td>Severe Pancreatic Insufficiency: &lt;100 mcg/g</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HPP</th>
<th>Pancreatic Polypeptide, Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>8014</td>
<td>Clinical Information: Pancreatic polypeptide (PP) is secreted by the pancreas in response to hypoglycemia, ingestion of food, or &quot;sham&quot; feeding (food is chewed, but not swallowed), secondary to vagal nerve stimulation. Secretion is blocked by vagotomy or atropine. The exact physiologic role of PP is undetermined, although the hormone is thought to be involved in exocrine pancreatic secretion and gallbladder emptying. Markedly elevated levels are often associated with endocrine tumors of the pancreas (eg, insulinoma, glucagonoma, PPoma: pancreatic polypeptide-secreting tumor of the pancreas) Patients with diabetes may also have elevated PP levels. A lack of response to sham feeding may indicate vagal nerve damage (eg, surgery-related nerve damage, autonomic nerve disorders). Extensive pancreatic destruction (eg, chronic pancreatitis, pancreatic cancer) may also result in low basal PP levels and a lack of response to sham feeding.</td>
</tr>
<tr>
<td></td>
<td>Useful For: Detection of pancreatic endocrine tumors Assessment of vagal nerve function after meal or sham feeding</td>
</tr>
<tr>
<td></td>
<td>Interpretation: High levels may be seen in pancreatic endocrine tumors, diabetes, and a nonfasting state. Markedly elevated levels may be seen in some pancreatic exocrine tumors. A normal response to a sham feeding consists of a rapid pancreatic polypeptide (PP) rise over baseline followed by a return to baseline. With vagal damage, no increase over baseline is seen.</td>
</tr>
<tr>
<td></td>
<td>Reference Values:</td>
</tr>
<tr>
<td></td>
<td>0-19 years: not established</td>
</tr>
<tr>
<td></td>
<td>20-29 years: &lt;228 pg/mL</td>
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<tr>
<td></td>
<td>30-39 years: &lt;249 pg/mL</td>
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<tr>
<td></td>
<td>40-49 years: &lt;270 pg/mL</td>
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</table>
50-59 years: <291 pg/mL
60-69 years: <312 pg/mL
70-79 years: <332 pg/mL
> or =80 years: not established


PAPN

Papain, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L   Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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<td>&gt; or =100</td>
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**PAPR 82810 Paprika, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease...
and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to
identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm
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allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Clinical References:** Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and
Management by Laboratory Methods. 21st edition. Edited by RA McPherson, MR Pincus. WB

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**Parafibromin, Immunostain, Technical Component Only**

**Clinical Information:** Parafibromin is a protein encoded by the HRPT2 oncosuppressor gene, and
the expression is reported to be decreased or absent in parathyroid carcinomas. Parafibromin is
expressed in the nucleus of benign parathyroids, parathyroid adenomas, and other normal tissues, but
shows loss of expression in parathyroid carcinomas, making it a good diagnostic tool to identify
parathyroid carcinomas and distinguish them from parathyroid adenomas.

**Useful For:**

**Interpretation:** The positive and negative controls are verified as showing appropriate
immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality
control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be
performed in the context of the patient's clinical history and other diagnostic tests by a qualified
pathologist.

**Clinical References:**
parafibromin distinguishes parathyroid carcinomas and hyperparathyroidism-jaw tumor (HPT-JT)
syndrome-related adenomas from sporadic parathyroid adenomas and hyperplasias. Am J Surg Pathol
parathyroid carcinoma-lone ranger or part of the posse? Int J Endocrinol 2010 3. Kim HK, Oh YL, Kim
SH, et al: Parafibromin immunohistochemical staining to differentiate parathyroid carcinoma from

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**Parainfluenza Virus (Types 1, 2, 3) Antibodies, Serum**

**Reference Values:**

REFERENCE RANGE: < 1:8

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
**INTERPRETIVE CRITERIA:**

- < 1:8 Antibody Not Detected
- > or =1:8 Antibody Detected

Single titers > or = 1:64 are indicative of recent infection. Titers of 1:8 to 1:32 may be indicative of either past or recent infection, since CF antibody levels persist for only a few months. A four-fold or greater increase in titer between acute and convalescent specimens confirms the diagnosis. After initial infection, antibody responses at a later date are often heterotopic and exhibit crossreactivity with other paramyxoviruses (e.g., mumps).

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**PAVAL 83380**

**Paraneoplastic, Autoantibody Evaluation, Serum**

**Clinical Information:** Paraneoplastic autoimmune neurological disorders reflect a patient's humoral and cellular immune responses to cancer. The cancer may be new or recurrent, is usually limited in metastatic volume, and is often occult by standard imaging procedures. Autoantibodies specific for onconeuronal proteins found in the plasma membrane, cytoplasm, and nucleus of neurons, glia, or muscle are generated in this immune response and serve as serological markers of paraneoplastic autoimmunity. Cancers recognized in this context most commonly are small-cell lung carcinoma, thymoma, ovarian (or related Mullerian) carcinoma, breast carcinoma, and Hodgkin lymphoma. Pertinent childhood neoplasms recognized thus far include neuroblastoma, thymoma, Hodgkin lymphoma, and chondroblastoma. An individual patient's autoantibody profile can predict a specific neoplasm with 90% certainty, but not the neurological syndrome. Four classes of autoantibodies are recognized in this evaluation:

- Neuronal nuclear (ANNA-1, ANNA-2, ANNA-3)
- Anti-glial/neuronal nuclear (AGNA-1; also known as Sox1)
- Neuronal and muscle cytoplasmic (PCA-1, PCA-2, PCA-Tr, CRMP-5, amphiphysin, and striational)
- Plasma membrane cation channel, calcium channels, P/Q-type and N-type calcium channel, dendrotoxin-sensitive potassium channels, and neuronal (ganglionic) and muscle nicotinic acetylcholine receptors (AChR). These autoantibodies are potential effectors of neurological dysfunction. Seropositive patients usually present with subacute neurological symptoms and signs such as encephalopathy; cerebellar ataxia; myelopathy; radiculopathy; plexopathy; or sensory, sensorimotor, or autoimmune neuropathy, with or without a neuromuscular transmission disorder: Lambert-Eaton syndrome, myasthenia gravis, or neuromuscular hyperexcitability. Initial signs may be subtle, but a subacute multifocal and progressive syndrome usually evolves. Sensorimotor neuropathy and cerebellar ataxia are common presentations, but the clinical picture in some patients is dominated by striking gastrointestinal dysmotility, limbic encephalopathy, basal ganglionitis, or cranial neuropathy (especially loss of vision, hearing, smell, or taste). Cancer risk factors include past or family history of cancer, history of smoking, or social or environmental exposure to carcinogens. Early diagnosis and treatment of the neoplasm favor less neurological morbidity and offer the best hope for survival.

**Useful For:** Serological evaluation of patients who present with a subacute neurological disorder of undetermined etiology, especially those with known risk factors for cancer. Directing a focused search for cancer Investigating neurological symptoms that appear in the course of, or after, cancer therapy, and are not explainable by metastasis. Differentiating autoimmune neuropathies from neurotoxic effects of chemotherapy. Monitoring the immune response of seropositive patients in the course of cancer therapy. Detecting early evidence of cancer recurrence in previously seropositive patients.

**Interpretation:** Antibodies directed at onconeuronal proteins shared by neurons, glia, muscle, and certain cancers are valuable serological markers of a patient's immune response to cancer. They are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. Several autoantibodies have a syndromic association, but no autoantibody predicts a specific neurological syndrome. Conversely, a positive autoantibody profile has 80% to 90% predictive value for a specific cancer. It is not uncommon for more than 1 paraneoplastic autoantibody to be detected, each predictive of the same cancer.

**Reference Values:**

**NEURONAL NUCLEAR ANTIBODIES**

Antineuronal Nuclear Antibody-Type 1 (ANNA-1)
<1:240
Antineuronal Nuclear Antibody-Type 2 (ANNA-2)
<1:240
Antineuronal Nuclear Antibody-Type 3 (ANNA-3)
<1:240
Anti-Glial/Neuronal Nuclear Antibody-Type 1 (AGNA-1)
<1:240

NEURONAL AND MUSCLE CYTOPLASMIC ANTIBODIES
Purkinje Cell Cytoplasmic Antibody, Type 1 (PCA-1)
<1:240
Purkinje Cell Cytoplasmic Antibody, Type 2 (PCA-2)
<1:240
Purkinje Cell Cytoplasmic Antibody, Type Tr (PCA-Tr)
<1:240
Amphiphysin Antibody
<1:240
CRMP-5-IgG
<1:240

Note: Titers lower than 1:240 are detectable by recombinant CRMP-5 Western blot analysis. CRMP-5 Western blot analysis will be done on request on stored serum (held 4 weeks). This supplemental testing is recommended in cases of chorea, vision loss, cranial neuropathy, and myelopathy. Call the Neuroimmunology Laboratory at 800-533-1710 or 507-266-5700 to request CRMP-5 Western blot.

Neuron-restricted patterns of IgG staining that do not fulfill criteria for amphiphysin, ANNA-1, ANNA-2, ANNA-3, AGNA-1, PCA-1, PCA-2, PCA-Tr, or CRMP-5-IgG may be reported as "unclassified antineuronal IgG." Complex patterns that include non-neuronal elements may be reported as "uninterpretable."

Striational (Striated Muscle) Antibodies
<1:120

CATION CHANNEL ANTIBODIES
N-Type Calcium Channel Antibody
< or =0.03 nmol/L
P/Q-Type Calcium Channel Antibody
< or =0.02 nmol/L
ACHR Ganglionic Neuronal Antibody
< or =0.02 nmol/L
Neuronal VGKC Autoantibody
< or =0.02 nmol/L

ACHR RECEPTOR ANTIBODIES
ACH Receptor (Muscle) Binding Antibody
< or =0.02 nmol/L
ACHR Receptor (Muscle) Modulating Antibody
0-20% loss of AChR

Neuromyelitis Optica (NMO)/Aquaporin-4-IgG FACS Assay
Negative

Paraneoplastic Western Blot
Negative
CRMP-5-IgG Western Blot
Negative
Amphiphysin Western Blot
Negative
N-Methyl-D-aspartate receptor (NMDA-R) CBA
Negative
IFA <1:120

2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid receptor (AMPA-R) CBA
Negative
IFA <1:120

Gamma-Amino Butyric acid-type B receptor (GABA-B-R) CBA
Negative
IFA <1:120

Leucine-Rich Glioma Inactivated Protein-1 IgG (LGI1) CBA
Negative

Contactin-Associated Protein-Like-2 IgG (CASPR2) CBA
Negative


Paraneoplastic, Autoantibody Evaluation, Spinal Fluid

Clinical Information: Several antineuronal and glial autoantibodies are recognized clinically as markers of a patient's immune response to specific cancers (paraneoplastic autoantibodies). Seropositive patients present with neurologic symptoms and signs in more than 90% of cases. The cancers are most commonly small-cell lung carcinoma, ovarian (or related mullerian) carcinoma, breast carcinoma, thymoma, or Hodgkin lymphoma. The cancers may be new or recurrent, are usually limited in metastatic volume, and are often occult by standard imaging procedures. Detection of the informative marker autoantibodies allows early diagnosis and treatment of the cancer, which may lessen neurological morbidity and improve survival. Serum is the preferred specimen for paraneoplastic autoantibodies. However, cerebrospinal fluid (CSF) results are sometimes positive when serum results are negative (especially for CRMP-5 and other inflammatory central nervous system autoimmunity). Additionally, CSF is more readily interpretable because it generally lacks the interfering nonorgan-specific antibodies that are common in the serum of patients with cancer. Because neurologists typically perform spinal taps in these patients, we recommend that CSF be submitted with serum, either for simultaneous testing or to be held for testing only if serum is negative. CRMP-5-IgG Western blot is also performed by specific request for more sensitive detection of CRMP-5-IgG. Testing should be requested in cases of subacute basal ganglionic disorders (chorea, Parkinsonism), cranial neuropathies (especially loss of vision, taste, or smell), and myelopathies.

Useful For: Aids in the diagnosis of paraneoplastic neurological autoimmune disorders related to carcinoma of lung, breast, ovary, thymoma, or Hodgkin lymphoma in spinal fluid specimens

Interpretation: Antibodies directed at onconeural proteins shared by neurons, glia, muscle, and certain cancers are valuable serological markers of a patient's immune response to cancer. They are not found in healthy subjects, and are usually accompanied by subacute neurological symptoms and signs. Several autoantibodies have a syndromic association, but no autoantibody predicts a specific neurological
syndrome. Conversely, a positive autoantibody profile has 80% to 90% predictive value for a specific cancer. It is not uncommon for more than one paraneoplastic autoantibody to be detected, each predictive of the same cancer. In patients with a history of tobacco use or other lung cancer risk, or if thymoma is suspected, PAVAL/Paraneoplastic Autoantibody Evaluation, Serum is also recommended.

Reference Values:

NEURONAL NUCLEAR ANTIBODIES
- Antineuronal Nuclear Antibody-Type 1 (ANNA-1) <1:2
- Antineuronal Nuclear Antibody-Type 2 (ANNA-2) <1:2
- Antineuronal Nuclear Antibody-Type 3 (ANNA-3) <1:2
- Anti-Glial/Neuronal Nuclear Antibody-Type 1 (AGNA-1) <1:2

NEURONAL AND MUSCLE CYTOPLASMIC ANTIBODIES
- Purkinje Cell Cytoplasmic Antibody, Type 1 (PCA-1) <1:2
- Purkinje Cell Cytoplasmic Antibody, Type 2 (PCA-2) <1:2
- Purkinje Cell Cytoplasmic Antibody, Type TR (PCA-TR) <1:2
- Amphiphysin Antibody <1:2
- Collapsin Response-Mediator Protein-5 Neuronal (CRMP-5-IgG) <1:2

Neuron-restricted patterns of IgG staining that do not fulfill criteria for amphiphysin, ANNA-1, ANNA-2, ANNA-3, AGNA-1, PCA-1, PCA-2, PCA-Tr, or CRMP-5-IgG may be reported as "unclassified antineuronal IgG." Complex patterns that include non-neuronal elements may be reported as "uninterpretable."

ISLET CELL ANTIBODIES
- Glutamic Acid Decarboxylase (GAD65) Antibody Assay ≤0.02 nmol/L

WESTERN BLOT
- Paraneoplastic Western Blot Negative
- CRMP-5-IgG Western Blot Negative
- Amphiphysin Western Blot Negative

- N-Methyl-D-aspartate receptor (NMDA-R)
  CBA: Negative
  IFA: <1:2
- 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid receptor (AMPA-R)
  CBA: Negative
  IFA: <1:2
- Gamma-Amino Butyric acid-type B receptor (GABA-B-R)
  CBA: Negative
  IFA: <1:2
- Leucine-Rich Glioma Inactivated Protein-1 IgG (LGI1) CBA Negative
- Contactin-Associated Protein-Like-2 IgG (CASPR2) CBA Negative
Neuromyelitis Optica (NMO)/Aquaporin-4-Igg FACS Assay
Negative

VGKC-Complex Antibody IPA
< or =0.02 nmol/L

**Clinical References:**

**Parasite Identification**

**Clinical Information:** Infectious diseases are spread and caused by a variety of macroscopic vectors. A wide array of macroscopic parasites (worms and ectoparasites) and parasite mimics or artifacts may be submitted for examination and identification. It is important to promptly and accurately identify these specimens so that the ordering physician can appropriately treat and counsel the patient.

**Useful For:** Gross identification of parasites (eg, worms) and arthropods (eg, ticks, bed bugs, lice, mites) Detecting or eliminating the suspicion of parasitic infection by identifying suspect material passed in stool or found on the body Supporting the diagnosis of delusional parasitosis Identifying ticks, including Ixodes species (the vector for Lyme disease)

**Interpretation:** A descriptive report is provided identifying the worm or arthropod. Worms and hard ticks are identified to the species level when possible, while other parasitic arthropods are identified to the genus level. Arthropods that do not cause human disease and parasite mimics resembling worms are reported as nonparasites or free living insects.

**Reference Values:**
A descriptive report is provided.


**Parasitic Examination**

**Clinical Information:** A variety of different parasites may be found in stool specimens, duodenal aspirates, and other intestinal specimens. These parasites may include protozoa (microscopic unicellular eukaryotes) and helminths (aka worms). Infection is often asymptomatic, but symptoms range from diarrhea and malnutrition, intestinal obstruction, and rarely, death. The most common intestinal reported parasites in stool specimens are Giardia intestinalis (aka Giardia duodenalis, Giardia lamblia) and Cryptosporidium species. Both parasites may cause watery diarrhea and are endemic in the United States. The best tests for these 2 common parasites are parasite-specific fecal antigen tests (GIAR / Giardia Antigen, Feces and CRYPS / Cryptosporidium Antigen, Feces). Other parasites are less commonly seen in the United States, and the stool parasitic exam is the appropriate test for their detection. See Parasitic Investigation of Stool Specimens Algorithm in Special Instructions for determining which test should be ordered based on the patient's exposure history and risk factors. If evaluating a patient for diarrhea, see Laboratory Testing for Infectious Causes of Diarrhea Algorithm.

**Useful For:** Detection and identification of parasitic protozoa and the eggs and larvae of parasitic
Interpretation: A positive result indicates the presence of the parasite but does not necessarily indicate that it is the cause of any symptoms. Some strains of protozoa are nonpathogenic and some helminths cause little or no illness.

Reference Values:
Negative
If positive, organism identified


Parathyroid Hormone (PTH) Immunostain, Technical Component Only

Clinical Information: Parathyroid hormone (PTH) staining is useful in identifying parathyroid glands in cases of hyperparathyroidism. Hyperproduction of parathyroid-like hormone may occur in association with lung tumors; such tumors may have reactivity with parathyroid hormone antibodies.

Useful For: Identification of parathyroid glands

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

Parathyroid Hormone (PTH), Serum

Clinical Information: Parathyroid hormone (PTH) is produced and secreted by the parathyroid glands, which are located along the posterior aspect of the thyroid gland. The hormone is synthesized as a 115-amino acid precursor (pre-pro-PTH), cleaved to pro-PTH and then to the 84-amino acid molecule, PTH (numbering, by universal convention, starting at the amino-terminus). The precursor forms generally remain within the parathyroid cells. Secreted PTH undergoes cleavage and metabolism to form carboxyl-terminal fragments (PTH-C), amino-terminal fragments (PTH-N), and mid-molecule fragments (PTH-M). Only those portions of the molecule that carry the amino terminus (ie, the whole molecule and PTH-N) are biologically active. The active forms have half-lives of approximately 5 minutes. The inactive PTH-C fragments, with half-lives of 24 to 36 hours, make up >90% of the total circulating PTH and are primarily cleared by the kidneys. In patients with renal failure, PTH-C fragments can accumulate to high levels. PTH 1-84 is also elevated in these patients, with mild elevations being considered a beneficial compensatory response to end organ PTH resistance, which is observed in renal failure. The serum calcium level regulates PTH secretion via negative feedback through the parathyroid calcium sensing receptor (CASR). Decreased calcium levels stimulate PTH
release. Secreted PTH interacts with its specific type II G-protein receptor, causing rapid increases in renal tubular reabsorption of calcium and decreased phosphorus reabsorption. It also participates in long-term calciosstatic functions by enhancing mobilization of calcium from bone and increasing renal synthesis of 1,25-dihydroxy vitamin D, which, in turn, increases intestinal calcium absorption. In rare inherited syndromes of parathyroid hormone resistance or unresponsiveness and in renal failure, PTH release may not increase serum calcium levels. Hyperparathyroidism causes hypercalcemia, hypophosphatemia, hypercalcuria, and hyperphosphaturia. Long-term consequences are dehydration, renal stones, hypertension, gastrointestinal disturbances, osteoporosis and sometimes neuropsychiatric and neuromuscular problems. Hyperparathyroidism is most commonly primary and caused by parathyroid adenomas. It can also be secondary in response to hypocalcemia or hyperphosphatemia. This is most commonly observed in renal failure. Long-standing secondary hyperparathyroidism can result in tertiary hyperparathyroidism, which represents the secondary development of autonomous parathyroid hypersecretion. Rare cases of mild, benign hyperparathyroidism can be caused by inactivating CASR mutations. Hypoparathyroidism is most commonly secondary to thyroid surgery, but can also occur on an autoimmune basis, or due to activating CASR mutations. The symptoms of hypoparathyroidism are primarily those of hypocalcemia, with weakness, tetany, and possible optic nerve atrophy.

**Useful For:** Diagnosis and differential diagnosis of hypercalcemia Diagnosis of primary, secondary, and tertiary hyperparathyroidism Diagnosis of hypoparathyroidism Monitoring end-stage renal failure patients for possible renal osteodystrophy

**Interpretation:** About 90% of the patients with primary hyperparathyroidism have elevated parathyroid hormone (PTH) levels. The remaining patients have normal (inappropriate for the elevated calcium level) PTH levels. About 40% of the patients with primary hyperparathyroidism have serum phosphorus levels <2.5 mg/dL and about 80% have serum phosphorus <3.0 mg/dL. An (appropriately) low PTH level and high phosphorus level in a hypercalcemic patient suggests that the hypercalcemia is not caused by PTH or PTH-like substances. An (appropriately) low PTH level with a low phosphorus level in a hypercalcemic patient suggests the diagnosis of paraneoplastic hypercalcemia caused by parathyroid related peptide (PTHRP). PTHRP shares N-terminal homology with PTH and can transactivate the PTH receptor. It can be produced by many different tumor types. A low or normal PTH in a patient with hypocalcemia suggests hypoparathyroidism, provided the serum magnesium level is normal. Low magnesium levels inhibit PTH release and action and can mimic hypoparathyroidism. Low serum calcium and high PTH levels in a patient with normal renal function suggest resistance to PTH action (pseudohypoparathyroidism type 1a, 1b, 1c, or 2) or, very rarely, bio-ineffective PTH. A limited number of the PTH-C fragments, which accumulate in renal failure, chiefly PTH 7-84, cross-react in this and other intact PTH assays. PTH 1-84 is also elevated in renal failure, with mild elevations being considered beneficial. Consequently, when measured with an intact PTH assay, concentrations of 1.5 to 3 times the upper limit of the healthy reference range appear to represent the optimal range for end-stage renal failure patients. Lower concentrations may be associated with adynamic renal bone disease, while higher levels suggest possible secondary or tertiary hyperparathyroidism, which can result in high-turnover renal osteodystrophy. Some patients with moderate hypercalcemia and equivocal phosphate levels, who have either mild elevations in PTH or (inappropriately) normal PTH levels, may be suffering from familial hypocalciuric hypercalcemia, which is due to inactivating CASR mutations. The molar renal calcium to creatinine clearance is typically <0.01 in these individuals. The condition can be confirmed by CASR gene mutation screening (CSRSP / Calcium Sensing Receptor [CASR] Gene, Full Gene Analysis).

**Reference Values:**
15-65 pg/mL
Reference values apply to all ages.

Parathyroid Hormone, Fine-Needle Aspiration Biopsy (FNAB)-Needle Wash

**Clinical Information:** Parathyroid hormone (PTH) is produced and secreted by the parathyroid glands, which are located along the posterior aspect of the thyroid gland. PTH analysis in rinse material obtained from fine-needle aspiration biopsies (FNAB) has gained popularity to discriminate thyroid tissues from enlarged parathyroid glands and also to facilitate parathyroid localization prior to surgery. Various groups have reported on the utility of this technique with specificity of 91% to 100% and sensitivity of 91% to 100%. Measuring PTH in the rinse material proved very useful in cases of nondiagnostic cytology. Comparing the results of the PTH rinse material with serum PTH is highly recommended. An elevated PTH in the serum could falsely elevate PTH in the washings if the rinse is contaminated with blood. In these cases, only PTH values significantly higher than the serum should be considered as true positives. Cytologic examination and measurement of PTH can be performed on the same specimen. To measure PTH, the fine-needle aspirate (FNA) needle is rinsed with a small volume of normal saline solution immediately after a specimen for cytological examination has been expelled from the needle for a smear or CytoTrap preparation. Specimen collection is critical for the performance of the assay and the needle should be rinsed with a minimal volume. Each FNA needle from a single biopsied area is washed with 0.1 to 0.5 mL of normal saline. The washes from a single area are pooled (final volume 1-1.5 mL). PTH levels are measured in the saline wash.

**Useful For:** An adjunct to cytology examination of fine-needle aspiration specimens to confirm or exclude presence of parathyroid tissue in the biopsied area

**Interpretation:** Parathyroid hormone (PTH) values less than 100 pg/mL suggest the biopsied site does not contain PTH-secreting tissue. PTH values greater than or equal to 100 pg/mL are suggestive of the presence PTH-secreting tissue at the site biopsied or along the needle track. This result is dependent on accurate sampling and a total needle wash volume of greater than or equal to 1.5 mL. This test should be interpreted in the context of the clinical presentation, imaging and cytology findings. If the results are discordant with the clinical presentation, a sampling error at the time of the biopsy should be considered.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

Parathyroid Hormone-Related Peptide (PTHrP), Plasma

**Clinical Information:** Hypercalcemia of malignancy is a common cause of hypercalcemia in hospitalized patients. Hypercalcemia of malignancy is typically not due to excess parathyroid hormone (PTH). In these disorders, PTH is usually suppressed due to elevated serum calcium concentrations. A variety of other mechanisms lead to inappropriate hypercalcemia in hypercalcemia of malignancy.
These include: -Impaired renal function due to a tumor or its treatment -Osteolytic activity within bony metastases -Release of calcemic cytokines by non-osteolytic bony metastases -Ectopic 1-alpha hydroxylase activity in tumor tissues -Secretion of humoral factors mimicking PTH action (humoral hypercalcemia of malignancy: HHM), usually associated with secretion of parathyroid hormone-related peptide (PTHrP) by the primary tumor (or more commonly its metastases) -Other as yet unknown factors

Frequently, a single cause cannot be pinpointed. Amongst the defined causes of the condition, PTHrP secretion is believed to be the most common culprit. PTHrP is a single monomeric peptide that exists in several isoforms, ranging from approximately 60 amino acids to 173 amino acids in size, which are created by differential splicing and posttranslational processing by prohormone convertases. PTHrP is produced in low concentrations by virtually all tissues. The physiological role of PTHrP remains incompletely understood. Its functions can be broadly divided into 5 categories, not all of which are present in all PTHrP isoforms or in all tissues: -Transepithelial calcium transport, particularly in the kidney and mammary gland -Smooth muscle relaxation in the uterus, bladder, gastrointestinal tract, and arterial wall -Regulation of cellular proliferation -Cellular differentiation and apoptosis of multiple tissues -As an indispensable component of successful pregnancy and fetal development (embryonic gene deletion is lethal in mammals) PTHrP's diverse functions are mediated through a range of different receptors, which are activated by different portions of PTHrP. Among the many receptors that respond to PTHrP is the PTH receptor, courtesy of the fact that 8 of the 13 N-terminal amino acids of PTH and of 3 common PTHrP isoforms are identical. Since most of PTHrP's actions in normal physiology are autocrine or paracrine, with circulating levels being very low, this receptor cross-talk only becomes relevant when there is extreme and sustained overproduction of PTHrP. This is seen occasionally in pregnancy, lactation and, rarely, in a variety of nonmalignant diseases. However, it is most commonly observed when tumors secrete PTHrP ectopically. In rough correlation with physiological production levels of PTHrP in the corresponding healthy tissues, ectopic PTHrP production is most commonly seen in carcinomas of breast, lung (squamous), head and neck (squamous), kidney, bladder, cervix, uterus, and ovary. Neuroendocrine tumors may also occasionally produce PTHrP. Most other carcinomas, sarcomas, and hemotolymphomatous malignancies only sporadically produce PTHrP, with the notable exceptions of T-cell lymphomas and myeloma. Patients with HHM may have increased PTHrP values before treatment. PTHrP level decreases and PTH level increases, accompanied by decreased serum calcium values, with successful treatment.

Useful For: Diagnostic workup of patients with suspected hypercalcemia of malignancy

Diagnostic workup of patients with hypercalcemia of unknown origin

Interpretation: Depending on the patient population, up to 80% of patients with malignant tumors and hypercalcemia will be suffering from humoral hypercalcemia of malignancy (HHM). Of these, 50% to 70% might have an elevated parathyroid hormone-related peptide (PTHrP) level. These patients will also usually show typical biochemical changes of excess parathyroid hormone (PTH)-receptor activation, namely, besides the hypercalcemia, they might have hypophosphatemia, hypercalcuria, hyperphosphaturia, and elevated serum alkaline phosphatase. Their PTH levels will typically be less than 30 pg/mL or undetectable. In patients with biochemical findings that suggest, but do not prove, primary hyperparathyroidism (eg, hypercalcemia, but normal or near-normal serum phosphate, and a PTH level that is within the population reference range but above 30 pg/mL), HHM should be considered as a diagnostic possibility, particularly if the patient is elderly, has a history of malignancy, or risk factors for malignancy. An elevated PTHrP level in such a patient is highly suggestive of HHM as the cause for the hypercalcemia.

Reference Values:

<2.0 pmol/L

Clinical References:
Parental Sample Prep for Prenatal Microarray Testing

Clinical Information: In order to interpret equivocal array results on a prenatal sample (amniotic fluid or chorionic villus), parental studies are performed to determine if the abnormality detected on the prenatal array is inherited or de novo. Maternal cell contamination testing is performed on the maternal blood and prenatal sample to detect the presence of maternal cells in the fetal sample.

Useful For: Preparing parental blood samples for possible confirmation testing if an abnormality is detected on the prenatal array sample DNA extraction of the maternal blood sample used for maternal cell contamination testing

Interpretation: No interpretation will be provided. This test is for sample processing only.

Reference Values: An interpretive report will be provided.

Parietal Cell Antibodies, IgG, Serum

Clinical Information: Pernicious anemia (PA) is characterized by atrophic body gastritis (ABG) and is the end state of a progressive disease known as autoimmune chronic atrophic gastritis. In this disease, immune-mediated inflammation leads to destruction of gastric parietal cells with the resultant loss of intrinsic factor production and the inability to absorb dietary vitamin B12. Diagnosis of PA involves demonstrating the presence of a macrocytic anemia in the context of vitamin B12 deficiency, as well as documenting positive autoantibody serology, specifically anti-parietal cell antibody (PCA) and intrinsic factor antibody (IFA). PCA bind to the alpha- and beta-subunits of the membrane-bound H+/K+-ATPase. In contrast, IFAs bind directly to intrinsic factor, blocking its ability to bind vitamin B12. Both PCAs and IFAs are useful diagnostic markers for PA. In a recently published study, PCAs were 81% sensitive and 90% specific for ABG, while IFAs were 27% sensitive and 100% specific. The study concluded that a combination of PCA and IFA testing was the optimal strategy for the evaluation of patients with suspected PA.

Useful For: Evaluating patients suspected of having pernicious anemia or immune-mediated deficiency of vitamin B12 with or without megaloblastic anemia

Interpretation: A positive result indicates the presence of IgG antibodies to H+/K+-ATPase and suggests the possibility of pernicious anemia (PA) or a related autoimmune disease. A negative result indicates no detectable IgG antibodies to H+/K+-ATPase; it does not rule out PA. An equivocal result is indeterminate.

Reference Values:
- Negative: < or =20.0 Units
- Equivocal: 20.1-24.9 Units
- Positive: > or =25.0 Units

Reference values apply to all ages.

Clinical References:

Parietaria judaica, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are
caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Parietaria officinalis, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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<td>4</td>
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<tr>
<td>5</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
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</tbody>
</table>

**Clinical References:** Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and
Management by Laboratory Methods. 21st edition. Edited by RA McPherson, MR Pincus. WB

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**Paroxetine, Serum**

**Clinical Information:** Paroxetine (Paxil and Paxil CR) is approved for treatment of depression.
Paroxetine is completely absorbed. Metabolites of paroxetine are inactive. Paroxetine metabolism is
carried out by cytochrome P450 (CYP) 2D6. Paroxetine can saturate CYP2D6 resulting in a nonlinear
relationship between dose and serum concentration. Paroxetine clearance is significantly affected by
reduced hepatic function, but only slightly by reduced renal function. A typical adult paroxetine dose is
30 mg per day. Paroxetine is 100% bioavailable, 95% protein bound, and the apparent volume of
distribution is 17 L/Kg. Time to peak serum concentration is 5 hours for the regular product and 8 hours
for the controlled release product. The elimination half-life is 20 hours. Half-life is prolonged in the
elderly and with cirrhosis.

**Useful For:** Monitoring paroxetine therapy Identifying noncompliance, although regular blood level
monitoring is not indicated in most patients Identifying states of altered drug metabolism when used in
conjunction with CYP2D6 genotyping

**Interpretation:** Steady-state serum concentrations associated with optimal response to paroxetine
are in the range of 30 to 120 ng/mL. The most common toxicities associated with excessive serum
concentration are asthenia, anticholinergic effects, anxiety, blurred vision, and changes in sexual
function. Toxic range: greater than 240 ng/mL.

**Reference Values:**

30-120 ng/mL

Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. Edited by CA Burtis, ER Ashwood,
Parrot Australian (Budgerigar) Feathers IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal/Borderline 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 High Positive 4 17.50 â€“ 49.99 Very High Positive 5 50.00 â€“ 99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**
<0.35 kU/L

Parsley IgG

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Parsley, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive

Particle Prep (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

PPPC
113354

Parvovirus B19 Antibodies, IgG and IgM, Serum
Clinical Information: Parvovirus B19 preferentially replicates in erythroid progenitor cells. Infection with parvovirus B19 occurs early in life and the virus is transmitted by respiratory secretion and occasionally by blood products. Antibody prevalence ranges from 2% to 15% in early adults. Parvovirus B19 may result in an asymptomatic infection or produce a wide spectrum of disease ranging from erythema infections (slapped cheek syndrome or fifth disease) in children to arthropathy, severe anemia, and systemic manifestations involving the central nervous system, heart, and liver depending on the immune competence of the host. Infection with parvovirus B19 in pregnant women may cause hydrops fetalis, congenital anemia, abortion, or stillbirth of the fetus. Parvovirus B19 is also the causative agent of persistent anemia usually, but not exclusively, in immunocompromised patients, transplant patients, and infants. Most acute infections with parvovirus B19 are diagnosed in the laboratory by serologically detecting IgG and IgM class antibodies with enzyme-linked immunosorbent assay testing.

Useful For: Serologic detection of recent or past parvovirus B19 infection

Interpretation: Parvovirus B19 IgM Parvovirus B19 IgG Interpretation Negative Negative Negative Implies no past infection or exposure to parvovirus B19. Patient may be susceptible to parvovirus B19 infection. Negative Positive Implies past exposure/infection and minimal risk of repeat parvovirus B19 infection. Equivocal Positive or negative May indicate current or recent parvovirus B19 infection. Recommendation to test a new convalescent specimen collected in 1 to 2 weeks Positive Positive Suggests current or recent parvovirus B19 infection Positive Negative or equivocal Suggests current or recent parvovirus B19 infection. Recommendation to test a new convalescent specimen collected in 1 to 2 weeks. The presence of IgM class antibodies suggests recent infection. The presence of IgG antibodies only is indicative of past exposure. Both IgG and IgM may be present at or soon after onset of illness and reach peak titers within 30 days. Because IgG antibody may persist for years, diagnosis of acute infection is made by the detection of IgM antibodies. The prevalence of parvovirus B19 IgG antibodies increases with age. The age-specific prevalence of antibodies to parvovirus is 2% to 9% of children under 5 years, 15% to 35% in children 5 to 18 years of age, and 30% to 60% in adults (19 years or older).

Reference Values:
IgG: Negative
IgM: Negative

Parvovirus B19 Antibodies, IgG, Serum

Clinical Information: Parvovirus B19 preferentially replicates in erythroid progenitor cells. Infection with parvovirus B19 occurs early in life and the virus is transmitted by respiratory secretion and occasionally by blood products. Antibody prevalence ranges from 2% to 15% in early adults. Parvovirus B19 may result in an asymptomatic infection or produce a wide spectrum of disease ranging from erythema infections (slapped cheek syndrome or fifth disease) in children to arthropathy, severe anemia, and systemic manifestations involving the central nervous system, heart, and liver depending on the immune competence of the host. Infection with parvovirus B19 in pregnant women may cause hydrops fetalis, congenital anemia, abortion, or stillbirth of the fetus. Parvovirus B19 is also the causative agent of persistent anemia usually, but not exclusively, in immunocompromised patients, transplant patients, and infants. Most acute infections with parvovirus B19 are diagnosed in the laboratory by serologically detecting IgG and IgM class antibodies with enzyme-linked immunosorbent assay testing.

Useful For: Serologic detection of recent or past parvovirus B19 infection

Interpretation: Parvovirus B19 IgM Parvovirus B19 IgG Interpretation Negative Negative Implies no past infection or exposure to parvovirus B19. Patient may be susceptible to parvovirus B19 infection Negative Positive Implies past exposure/infection and minimal risk of repeat parvovirus B19 infection Equivocal Positive or negative May indicate current or recent parvovirus B19 infection. Recommendation to test a new, convalescent specimen collected in 1 to 2 weeks Positive Positive Suggests current or recent parvovirus B19 infection Positive Negative or equivocal Suggests current or recent parvovirus B19 infection. Recommendation to test a new, convalescent specimen collected in 1 to 2 weeks. The presence of IgM class antibodies suggests recent infection. The presence of IgG antibodies only is indicative of past exposure. Both IgG and IgM may be present at or soon after onset of illness and reach peak titers within 30 days. Because IgG antibody may persist for years, diagnosis of acute infection is made by the detection of IgM antibodies. The prevalence of parvovirus B19 IgG antibodies increases with age. The age-specific prevalence of antibodies to parvovirus is 2% to 9% of children under 5 years, 15% to 35% in children 5 to 18 years of age, and 30% to 60% in adults (19 years or older).

Reference Values: Only orderable as part of a profile. For more information see PARVS / Parvovirus B19 Antibodies, IgG and IgM, Serum.

Parvovirus B19 Antibody Interpretation

Reference Values: Only orderable as part of a profile. For further more information see PARVS / Parvovirus B19 Antibodies, IgG and IgM, Serum.

Parvovirus B19 Antibody, IgM, Serum

Clinical Information: Parvovirus B19 preferentially replicates in erythroid progenitor cells. Infection with parvovirus B19 occurs early in life and the virus is transmitted by respiratory secretion and occasionally by blood products. Antibody prevalence ranges from 2% to 15% in early adults. Parvovirus B19 may result in an asymptomatic infection or produce a wide spectrum of disease ranging from erythema infections (slapped cheek syndrome or fifth disease) in children to arthropathy, severe anemia, and systemic manifestations involving the central nervous system, heart, and liver depending on the immune competence of the host. Infection with parvovirus B19 in pregnant women may cause hydrops fetalis, congenital anemia, abortion, or stillbirth of the fetus. Parvovirus B19 is also the causative agent of persistent anemia usually, but not exclusively, in immunocompromised patients,
transplant patients, and infants. Most acute infections with parvovirus B19 are diagnosed in the laboratory by serologically detecting IgG and IgM class antibodies with enzyme-linked immunosorbent assay testing.

**Useful For:** Serologic detection of recent or past parvovirus B19 infection

**Interpretation:** Parvovirus B19 IgM Parvovirus B19 IgG Interpretation Negative Negative Implies no past infection or exposure to parvovirus B19. Patient may be susceptible to parvovirus B19 infection Negative Positive Implies past exposure/infection and minimal risk of repeat parvovirus B19 infection Equivocal Positive or negative May indicate current or recent parvovirus B19 infection. Recommendation to test a new, convalescent specimen collected in 1 to 2 weeks Positive Positive Suggests current or recent parvovirus B19 infection Positive Negative or equivocal Suggests current or recent parvovirus B19 infection. Recommendation to test a new, convalescent specimen collected in 1 to 2 weeks. The presence of IgM class antibodies suggests recent infection. The presence of IgG antibodies only is indicative of past exposure. Both IgG and IgM may be present at or soon after onset of illness and reach peak titers within 30 days. Because IgG antibody may persist for years, diagnosis of acute infection is made by the detection of IgM antibodies. The prevalence of parvovirus B19 IgG antibodies increases with age. The age-specific prevalence of antibodies to parvovirus is 2% to 9% of children under 5 years, 15% to 35% in children 5 to 18 years of age, and 30% to 60% in adults (19 years or older).

**Reference Values:**
Only orderable as part of a profile. For more information see PARVS / Parvovirus B19 Antibodies, IgG and IgM, Serum.

**Negative**

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**Parvovirus B19, Molecular Detection, PCR**

**Clinical Information:** Parvovirus B19 preferentially replicates in erythroid progenitor cells.(1) Infection with parvovirus B19 occurs early in life and the virus is transmitted by respiratory secretion and occasionally by blood products. Antibody prevalence ranges from 2% to 15% in early adults.(1) Parvovirus B19 may result in an asymptomatic infection or produce a wide spectrum of disease ranging from erythema infections (slapped cheek syndrome or fifth disease) in children to arthropathy, severe anemia, and systemic manifestations involving the central nervous system, heart, and liver depending on the immune competence of the host.(2,3) Infection with parvovirus B19 in pregnant women may cause hydrops fetalis, congenital anemia, abortion, or stillbirth of the fetus.(4) Parvovirus B19 is also the causative agent of persistent anemia usually, but not exclusively, in immunocompromised patients, transplant patients, and infants. Most acute infections with parvovirus B19 are diagnosed in the laboratory by serologically detecting IgG and IgM class antibodies with enzyme-linked immunosorbent assay testing.

**Useful For:** Diagnosing parvovirus B19 infection

**Interpretation:** A positive result indicates that parvovirus B19 DNA is present in the clinical sample. However, a positive result does not differentiate between actively replicating virus, transient infection that may be asymptomatic, or simply the presence of remnant viral nucleic acid. A negative result suggests the absence of parvovirus B19 infection.

**Reference Values:**
Negative

**Clinical References:**
Parvovirus B19, Molecular Detection, PCR, Plasma

Clinical Information: Parvovirus B19 preferentially replicates in erythroid progenitor cells. Infection with parvovirus B19 occurs early in life and the virus is transmitted by respiratory secretion and occasionally by blood products. Antibody prevalence ranges from 2% to 15% in early adults.

Parvovirus B19 may result in an asymptomatic infection or produce a wide spectrum of disease ranging from erythema infections (slapped cheek syndrome or fifth disease) in children to arthropathy, severe anemia, and systemic manifestations involving the central nervous system, heart, and liver, depending on the immune competence of the host. Infection with parvovirus B19 in pregnant women may cause hydrops fetalis, congenital anemia, abortion, or stillbirth of the fetus. Parvovirus B19 is also the causative agent of persistent anemia usually, but not exclusively, in immunocompromised patients, transplant patients, and infants. Most acute infections with parvovirus B19 are diagnosed in the laboratory by serologically detecting IgG and IgM class antibodies with enzyme-linked immunosorbent assay testing.

Useful For: Diagnosing parvovirus B19 infection in plasma specimens

Interpretation: A positive result indicates that parvovirus B19 DNA is present in the clinical sample. However, a positive result does not differentiate between actively replicating virus, transient infection that may be asymptomatic, or simply the presence of remnant viral nucleic acid. A negative result suggests the absence of parvovirus B19 infection.

Reference Values: Not applicable

Clinical References:

Parvovirus Immunostain, Technical Component Only

Clinical Information: Parvovirus infection is implicated as a cause of hydrops fetalis and may result in spontaneous abortions. It has also been implicated in chronic hemolytic anemia. The virus is associated with erythema infectiosum (Fifth disease) in children and acute arthritis in adults.

Useful For: Identification of parvovirus infection

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:
**Passion Fruit, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

accurate results. Stained slides and paraffin blocks received are reviewed in conjunction with the clinical history provided, laboratory findings, radiographic findings (if applicable), and sending pathologist's report or letter. If additional special stains or studies are needed, the results are included in the final interpretive report. In some cases, electron microscopy and other special procedures are utilized as required. A variety of ancillary studies are available (eg, cytochemistry, immunohistochemistry, immunofluorescence, electron microscopy, mass spectrometry, cytogenetics, and molecular genetics) to aid in establishing a diagnosis. These ancillary studies are often expensive and labor intensive, and are most efficiently utilized and interpreted in the context of the morphologic features. It is our goal to provide the highest possible level of diagnostic consultative service, while trying to balance optimal patient care with a cost-conscious approach to solving difficult diagnostic problems.

**Useful For:** Obtaining a rapid, expert second opinion on specimens referred by the primary pathologist Obtaining special studies not available locally

**Interpretation:** Results of the consultation are reported in a formal pathology report that includes a description of ancillary test results (if applicable) and an interpretive comment. When the case is completed, results are communicated by a phone call. The formal pathology report is faxed. In our consultative practice, we strive to bring the customer the highest quality of diagnostic pathology, in all areas of expertise, aiming to utilize only those ancillary tests that support the diagnosis in a cost-effective manner, and to provide a rapid turnaround time for diagnostic results.

**Reference Values:**
The laboratory will provide a pathology consultation.

### PAX5

**PAX-5 Immunostain, Technical Component Only**

**Clinical Information:** PAX-5, also known as B-cell-specific activator protein (BSAP), is a B-cell specific transcription factor expressed during differentiation. Plasma cells (terminally differentiated B cells) are usually negative. Used in the classification of B-cell lymphomas.

**Useful For:** Classification of lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

### PAX8

**PAX8 Immunostain, Technical Component Only**

**Clinical Information:** PAX8 is a member of the paired box gene (PAX) family of transcription factors involved in kidney cell and thyroid development. PAX8 has been shown to be expressed in a high percentage of renal neoplasms, including both malignant renal cell carcinomas and benign renal tumors (oncocytomas). PAX8 has also been reported to be expressed in ovarian carcinomas.
Useful For: Aids in the identification of renal cell carcinomas, as well as papillary thyroid carcinomas and tumors of Mullerian origin

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


PCA3 (Prostate Cancer Antigen 3)

Clinical Information: Prostate cancer antigen 3 (PCA3, also known as Differential Display Code 3 or DD3) is a prostate-specific gene that was present in 95% of prostate cancer samples initially studied, and significantly over-expressed in cancer versus benign tissue. PCA3 is known to be a non-coding messenger ribonucleic acid (mRNA) with no resultant protein. Clinically, PCA3 mRNA is detectable in the urine and appears to be independent of prostate volume and serum PSA. The PCA3 urinary assay is reported out as a ratio of PCA3 mRNA to PSA mRNA.

Reference Values:
A score less than 25 is considered negative
A score greater than or equal to 25 is considered positive

PDGFB (22q13), Dermatofibrosarcoma Protuberans/Giant Cell Fibroblastoma, FISH, Tissue

Clinical Information: Dermatofibrosarcoma protuberans (DFSP) is a superficial, low-grade sarcoma genetically characterized by the unbalanced chromosomal translocation t(17;22)(q21;q13), usually in the form of a supernumerary ring chromosome. The product of this chromosomal translocation is the chimeric gene COL1A1-PDGFB. Rearrangements of this gene have been detected in approximately 90% of DFSP and its related infantile form, giant cell fibroblastoma, but not in other tumors.

Useful For:Confirming the diagnosis of dermatofibrosarcoma protuberans (DFSP)/giant cell fibroblastoma (GCF) and excluding other spindle neoplasms that closely simulate the DFSP histology, including dermatofibroma (benign fibrous histiocytoma), neurofibroma, spindle cell lipoma, and a
variety of other benign and malignant spindle cell neoplasms

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for the PDGFB FISH probe. A positive result is consistent with rearrangement/amplification of the PDGFB gene locus on 22q13 and supports the diagnosis of dermatofibrosarcoma protuberans (DFSP) or giant cell fibroblastoma (GCF). A negative result is consistent with no rearrangement/amplification of the PDGFB gene locus on 22q13. However, this result does not exclude the diagnosis of DFSP or GCF. The degree of PDGFB copy gain/amplification/rearrangement varies in individual tumors and among different cells in the same tumor. It is not currently known if patients with different levels of rearrangement/amplification have the same prognosis and response to therapy.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**PDG12**

**PDGFRA Exon 12, Mutation Analysis**

**Clinical Information:** Occasional cases of gastrointestinal stromal tumors (GIST) can harbor mutations in PDGFRA, a gene structurally related to KIT. The frequency and type of mutations vary among these tumors and portent distinct clinical implications. The ordering physician is responsible for the diagnosis and management of disease and decisions based on the data provided.

**Useful For:** Diagnosis and management of patients with gastrointestinal stromal tumors or other related tumors Identification of a mutation in exon 12 of the PDGFRA gene This is not appropriate for evaluation of hypereosinophilic syndrome (HES) and systemic mast cell disease involving the FIP1L1-PDGFR fusion

**Interpretation:** Results are reported as positive, negative, or failed. A negative result does not rule out the presence of a mutation.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
**PDGFRA Exon 14, Mutation Analysis**

**Clinical Information:** Occasional cases of gastrointestinal stromal tumors (GIST) can harbor mutations in PDGFRA, a gene structurally related to KIT. The frequency and type of mutations vary among these tumors and portent distinct clinical implications. The ordering physician is responsible for the diagnosis and management of disease and decisions based on the data provided.

**Useful For:** Diagnosis and management of patients with gastrointestinal stromal tumors or other tumors Identification of a mutation in exon 14 of the PDGFRA gene

**Interpretation:** Results are reported as positive, negative, or failed. A negative result does not rule out the presence of a mutation.

**Reference Values:** An interpretative report will be provided.

**Clinical References:**

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**PDGFRA Exon 18, Mutation Analysis**

**Clinical Information:** Occasional cases of gastrointestinal stromal tumors (GIST) can harbor mutations in PDGFRA, a gene structurally related to KIT. The frequency and type of mutations vary among these tumors and portent distinct clinical implications. The ordering physician is responsible for the diagnosis and management of disease and decisions based on the data provided.

**Useful For:** Diagnosis and management of patients with gastrointestinal stromal tumors or other related tumors Identification of a mutation in exon 18 of the PDGFRA gene

**Interpretation:** Results are reported as positive, negative, or failed. A negative result does not rule out the presence of a mutation.

**Reference Values:** An interpretative report will be provided.

**Clinical References:**

8. Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
PDGFRB/TEL Translocation (5;12) for Chronic Myelomonocytic Leukemia (CMML), FISH

Clinical Information: Platelet-derived growth factor receptor-beta (PDGFRB) produces a tyrosine kinase involved in cell proliferation. Translocation-ets-leukemia protein (encoded by the gene ETV6) is a gene transcription protein that is frequently rearranged in leukemias. A 5;12 translocation, t(5;12)(q33;p13), results in a fusion product (PDGFRB/ETV6) that is seen in approximately 1% to 2% of patients diagnosed with chronic myelomonocytic leukemia. Patients with this translocation often have associated hypereosinophilia. Imatinib mesylate is an inhibitor of tyrosine kinases, including PDGFRB. Patients with the 5;12 translocation are reportedly responsive to imatinib mesylate; upon treatment, they usually go into complete remission.

Useful For: Identifying patients with chronic myelomonocytic leukemia and other hematologic disorders who may be responsive to imatinib mesylate Identifying and tracking chromosome abnormalities and response to therapy

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff. The presence of a positive clone supports a diagnosis of malignancy. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

Reference Values: An interpretive report will be provided.


Pea Black-Eyed/Cow Pea (Vigna sinensis) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values: <0.35 kU/L

Pea Green IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values: <2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.
**Peach IgG**

**Interpretation:** mcg/mL of IgG  
Lower Limit of Quantitation: 2.0  
Upper Limit of Quantitation: 200

**Reference Values:**  
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

---

**Peach, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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</tr>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference</td>
</tr>
</tbody>
</table>

*Reference values apply to all ages.*

**Peanut IgG**

**Interpretation:** mcg/mL of IgG  
Lower Limit of Quantitation* 2.0  
Upper Limit of Quantitation** 200

**Reference Values:**  
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Peanut IgG4**

**Interpretation:** mcg/mL of IgG4  
Lower Limit of Quantitation 0.15  
Upper Limit of Quantitation 30.0

**Reference Values:**  
<0.15 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicated immunologic sensitization to the food allergen in question.

**Peanut, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children younger than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins), followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens that may be responsible for allergic disease or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
**Class IgE kU/L  Interpretation**

0    Negative
0.10-0.34  Borderline/Equivocal
0.35-0.69  Equivocal
0.70-3.49  Positive
3.50-17.4  Positive
17.5-49.9  Strongly positive
50.0-99.9  Strongly positive
> or ≥ 100  Strongly positive

Reference values apply to all ages.


**PEANT 64756**

**Peanut, IgE with Reflex to Peanut Components, IgE, Serum**

**Clinical Information:** Peanut allergy is one of the most common food allergies in the United States, with an estimated prevalence of approximately 1% to 2%.(1) The clinical symptoms of peanut allergy may range from relatively mild, such as rhinorrhea, pruritus, or nausea, to an anaphylactic reaction that is systemic and potentially life-threatening. The diagnosis of peanut allergy is dependent upon the presence of compatible clinical symptoms in the context of peanut exposure, with support from identification of peanut-specific IgE antibodies, either by skin testing or in vitro serology testing. In vitro testing has generally focused on assessing for the presence of total peanut IgE antibodies. These antibodies are identified by immunoassay in which the capture allergen is an extract prepared from natural peanut raw material. Most studies have demonstrated a correlation between total peanut IgE antibodies and an increased likelihood of a clinical allergic response. However, some patients with significantly elevated concentrations of total peanut IgE antibodies do not have any reaction when administered a peanut oral food challenge. In some cases, this may be due to the presence of an IgE antibody specific for a nonallergenic protein present within the peanut extract. This is the basis of component allergen testing, in which the presence of IgE antibodies specific for individual proteins, namely Ara h 1, Ara h 2, Ara h 3, Ara h 8, and Ara h 9, within the peanut extract are assessed. Ara h 1, 2, and 3 are seed storage proteins, and are the most relevant for evaluation of suspected peanut allergy.(2,3) Ara h 2, in particular, has the best sensitivity and specificity for clinically relevant peanut allergic disease. Ara h 1, 2, and 3-specific IgEs also tend to be associated with more severe allergic reactions. Ara h 9 is a member of the lipid transfer protein (LTP) family. LTPs are ubiquitous throughout the plant kingdom, and are also extremely homologous. IgE antibodies specific for Ara h 9 may be associated with allergic reactions upon peanut ingestion, although published data on this is not conclusive.(4) In addition, because of the significant sequence homology, cross-reactivity of IgE antibodies may be observed between Ara h 9 and LTPs in commonly consumed plants such as peaches, apples, and plums. Lastly, Ara h 8 is a homologue of the birch pollen allergen Bet v 1. IgE antibodies against Ara h 8 are generally associated with milder peanut allergies and may be seen in the context of birch pollen sensitization.(5)

**Useful For:** Evaluation of patients with suspected peanut allergy Evaluation of patients with possible peanut cross-reactivity

**Interpretation:** Negative for total peanut IgE: -Negative IgE results for total peanut may indicate a lack of sensitization to peanut. Because IgE antibodies specific for total peanut are not detectable, testing for peanut components is not performed. Positive for total peanut IgE/negative for peanut component IgE: -Positive IgE results for total peanut in the absence of detectable IgE responses to any peanut components may indicate a low to moderate sensitization to peanut. Correlation with patient
history of allergic or anaphylactic responses to peanut is recommended. Positive for total peanut IgE/positive for peanut component IgE: -Positive IgE results to the storage proteins Ara h 1, Ara h 2, and Ara h 3 in the context of a positive IgE result for total peanut may be associated with sensitization to peanut, with increased risk for allergic reaction upon exposure to peanut, and/or with a stronger risk for a systemic reaction. -Positive IgE results to Ara h 8 in the context of a positive IgE result for total peanut, but with negative antibodies to Ara h 1, Ara h 2, and Ara h 3, may be associated with cross-reactivity with birch and birch-related tree pollens and/or with an increased risk of a localized allergic reaction. -Positive IgE results to Ara h 9 have been associated with both systemic and localized reactions, and with cross-reactivity to peach and peach-related fruits.

### Reference Values:

<table>
<thead>
<tr>
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<th>Interpretation</th>
</tr>
</thead>
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<td>Negative</td>
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<tr>
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<td>2</td>
<td>0.70-3.49</td>
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<td>3</td>
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<td>5</td>
<td>50.0-99.9</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**Reference values apply to all ages.**

### Clinical References:


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**FPEAR**

### Pear IgG

**Interpretation:** mcg/mL of IgG

**Lower Limit of Quantitation:** 2.0

**Upper Limit of Quantitation:** 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**PEAR**

### Pear, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and
clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of
sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and
bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat
proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease
and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to
identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm
sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity
of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with
the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<td>3.50-17.4 Positive</td>
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<tr>
<td>5</td>
<td>50.0-99.9 Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**Clinical References:** Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and
Management by Laboratory Methods. 21st edition. Edited by RA McPherson, MR Pincus. WB

**PCANH 62600**  
**Pecan Hickory, IgE**  
**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are
cased by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from

**FPCFG 57688**  
**Pecan Food IgG**  
**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

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<th>mcg/mL</th>
<th>Reference</th>
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<tr>
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<td>Negative</td>
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</table>

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical
utility of food-specific IgG tests has not been established. These tests can be used in special clinical
situations to select foods for evaluation by diet elimination and challenge in patients who have
food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be
taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in
question. This test should only be ordered by physicians who recognize the limitations of the test.
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergic disease and defining the allergens responsible for eliciting signs and symptoms. Identifying allergens which may be responsible for allergic disease and/or anaphylactic episode, confirming sensitization to particular allergens prior to beginning immunotherapy, and investigating the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<tr>
<td>6</td>
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</table>

Reference values apply to all ages.


**PEC 82880**

**Pecan-Food, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm
sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</table>

Reference values apply to all ages.


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**PAS38**

**Pediatric Allergy Screen 3 to 8 Years, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and /or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>Class</th>
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<tbody>
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<tr>
<td>1</td>
<td>0.35-0.69</td>
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</tbody>
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PAS3 83345

Pediatric Allergy Screen

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.

**Pediatric Allergy Screen >8 Years, Serum**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<td>Negative</td>
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<tr>
<td>1</td>
<td>0.35-0.69</td>
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<td>2</td>
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<td>17.5-49.9</td>
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<td>50.0-99.9</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Penicillin G, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and
wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>IgE kU/L</th>
<th>Interpretation</th>
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<td>0</td>
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<td>Negative</td>
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<tr>
<td>1</td>
<td>0.35-0.69</td>
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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
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<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
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<td>4</td>
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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

*Reference values apply to all ages.*


---

**Penicillin V, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
Reference Values:
Class IgE kU/L Interpretation
0  Negative
1  0.35-0.69 Equivocal
2  0.70-3.49 Positive
3  3.50-17.4 Positive
4  17.5-49.9 Strongly positive
5  50.0-99.9 Strongly positive
6  > or =100 Strongly positive Reference values apply to all ages.


Penicillum chrysogenum, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0  Negative
1  0.35-0.69 Equivocal
2  0.70-3.49 Positive
3  3.50-17.4 Positive
4  17.5-49.9 Strongly positive
5  50.0-99.9 Strongly positive

PENTs 8239

Pentobarbital, Serum

Clinical Information: Pentobarbital is a short-acting barbiturate with anticonvulsant and sedative-hypnotic properties. Uses include sedation induction; relief of preoperative anxiety; control of status epilepticus or seizures resulting from meningitis, tetanus, alcohol withdrawal, poisons, chorea, or eclampsia; and induction of coma in the management of cerebral ischemia and increased intracranial pressure that may follow stroke or head trauma.(1,2) Pentobarbital is administered orally, parenterally, and rectally. The duration of hypnotic effect is about 1 to 4 hours. The drug distributes throughout the body, with about 35% to 45% of a dose bound to plasma proteins in the blood. Metabolism takes place in the liver via oxidation to the inactive metabolite hydroxypentobarbital. Elimination is biphasic; half-life is about 4 hours in the first phase, and 35 to 50 hours in the second phase. Excretion occurs through the urine, mainly as glucuronide conjugates of metabolites, with only about 1% excreted as unchanged drug.(1,2) Tolerance to pentobarbital's hypnotic effects occurs after about 2 weeks of continuous dosing.

Useful For: Monitoring of pentobarbital therapy treatment

Interpretation: Pentobarbital concentrations above 10 mcg/mL have been associated with toxicity.

Reference Values:
Therapeutic range
Hypnotic: 1-5 mcg/mL
Therapeutic coma: 20-50 mcg/mL
Reducing intracranial pressure: 30-40 mcg/mL
This degree of sedation requires artificial respiratory support.
Toxic concentration: >10 mcg/mL


F PBPG 57657

Pepper Bell/Paprika IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

FPB LG 57645

Pepper Black IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200
Reference Values:
<2 mcg/mL.

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Pepper Cayenne (Capsicum frutescens) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:
<0.35 kU/L

**Pepper Chili IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:
<2 mcg/mL.

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Pepsin A Assay**

**Reference Values:**
Protein Unit = mg/mL
One unit of pepsin A = 0.1 ng/mL
Pepsin A by Elisa assay

Pepsin A Reference Range (Units):
<3.0 negative
3-50 weak to moderate positive
>50 strong positive

**Pepsinogen I**

**Reference Values:**
28 - 100 ng/mL
(mean 40)
Perampanel, Serum

**Interpretation:** Synonym(s): Fycompa Daily administration of 6 mg perampanel resulted in peak plasma concentrations averaging 460 ng/mL at approximately 1.3 hours post dose. Peak concentrations following a single 12 mg dose of perampanel averaged 800 ng/mL.

Perch Ocean

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

Percocet, Urine

**Reference Values:**

Percocet, Urine:

Acetaminophen: ug/mL
Note: Analysis performed on urine.

Reference ranges have not been established for urine specimens.

Oxycodone: ng/mL
Oxymorphone: ng/mL

Peripheral Blood (Bill Only)

**Reference Values:**

This test is for billing purposes only.
This is not an orderable test.

Peripheral Blood, TC (Bill Only)

**Reference Values:**

This test is for billing purposes only.
This is not an orderable test.

Peripheral Nerve Pathology Consultation

**Clinical Information:** Nerve biopsies provide information about nerve fibers and the interstitium of the nerve. Neuropathic abnormalities include decreased density of myelinated fibers, segmental demyelination, and axonal degeneration. Some possible interstitial abnormalities that affect nerves include necrotizing vasculitis and amyloidosis. This consultation is for fixed tissue, slides, or blocks.

**Useful For:** Evaluating diseases of the nerve and disorders that affect nerve function

**Interpretation:** The clinical and neurological history is reviewed with the interpretation of the biopsy. The histologic slides, special stains, and history, along with the physician's report are correlated by a neuromuscular pathologist. An interpretive report will be provided.

**Reference Values:**
Peripheral Neuropathy Expanded Panel by Next-Generation Sequencing (NGS)

Clinical Information: Inherited peripheral neuropathies are a relatively common diverse group of disorders with heterogeneous genetic causes. Due to the considerable overlap in the clinical phenotypes of various neuropathies, it is often difficult to distinguish these specific inherited disorders from sporadic, idiopathic, or acquired forms of neuropathy without genetic testing. Based on the pattern of inheritance and nerve conduction studies, there are 3 major categories of inherited peripheral neuropathies with isolated nerve involvement: 1) hereditary motor and sensory neuropathy (HMSN), also referred as Charcot Marie Tooth (CMT); 2) hereditary sensory and autonomic neuropathy (HSAN), or hereditary sensory neuropathy (HSN), if autonomic dysfunction is absent; and 3) distal hereditary motor neuropathy (dHMN). Inherited peripheral neuropathies may also show involvement of the central nervous system (brain or spinal cord), as in hereditary spastic paraplegia (HSP) with neuropathy (complicated form, also referred to as HSMN type 5) or be part of a systemic syndromic or metabolic disorder. Given the considerable phenotypic overlap and the broad genetic heterogeneity of inherited peripheral neuropathies a comprehensive diagnostic genetic test is useful to establish the genetic cause in these clinical groups. See Targeted Genes Interrogated by Peripheral Neuropathy Expanded Panel in Special Instructions for details regarding the targeted genes identified by this test.

Useful For: Diagnosis of inherited peripheral neuropathies with isolated nerve involvement or associated with other organ system or associated with metabolic syndromes with known causal genes. A second-tier test for patients in whom previous targeted gene mutation analyses for specific inherited peripheral neuropathy-related genes were negative. Identifying mutations within genes known to be associated with inherited peripheral neuropathy, allowing for predictive testing of at-risk family members.

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


Peripheral Smear Interpretation

Clinical Information: Under normal conditions, the morphology and proportion of each blood cell type is fairly consistent in corresponding age groups. The morphology and proportion of each blood cell type may change in various hematologic diseases. Differential leukocyte count/special smear evaluation is helpful in revealing the changes in morphology or proportion of each cell type in the peripheral blood.

Useful For: Detecting disease states or syndromes of the white blood cells, red blood cells, or platelet cell lines of a patient's peripheral blood.

Interpretation: The laboratory will provide an interpretive report of percentage of white cells and, if appropriate, evaluation of white cells, red cells, and platelets.
**TP63F**

**Peripheral T-Cell Lymphoma (PTCL), TP63 (3q28)**

**Rearrangement, FISH, Tissue**

**Clinical Information:** Peripheral T-cell lymphomas (PTCL) are malignant neoplasms of mature T-lymphocyte origin that account for 10% to 15% of all non-Hodgkin lymphomas. Most subtypes have a slight male predominance and occur in older individuals (>50 years). Some subtypes, particularly ALK-positive anaplastic large cell lymphoma (ALCL), are seen in younger patients. Over 15 subtypes of PTCL are recognized in the World Health Organization classification system. These types differ in their clinical presentation, morphologic appearance, immunophenotype, genetics, and in some cases, prognostic and therapeutic implications. The relative distribution of subtypes varies geographically. In the United States, the most common types of systemic PTCL are PTCL, not otherwise specified (NOS); angioimmunoblastic T-cell lymphoma (AITL); and ALCL (both ALK-positive and ALK-negative types). In diagnostic practice, PTCL must be distinguished from reactive T-cell proliferations as well as from hematopoietic neoplasms of non-T-cell lineage and nonhematopoietic tumors. In addition, PTCL must be subclassified to the extent possible. The designation PTCL, NOS, is reserved for PTCL that do not meet criteria for inclusion in one of the other, more specific categories, which occurs in a significant fraction of PTCL. Recurrent translocations involving the TP63 gene on 3q28 have been described in PTCL. In one series of 190 PTCL of various subtypes, TP63 translocations were seen in 5.8%. However, these were not distributed equally among PTCL subtypes, occurring in 9.4% of PTCL, NOS; 12.5% of ALK-negative ALCL; and 10.5% of primary cutaneous ALCL. No cases of ALK-positive ALCL, AITL, or other PTCL subtypes were found to have TP63 translocations. In 63.6% of cases with TP63 translocations, the translocation partner gene was identified to be TBL1XR1. Other partners also exist. TP63 translocations have been shown to encode fusion transcripts that give rise to fusion proteins homologous to delta-N isoforms of wild-type p63. In 1 study, the presence of TP63 translocations among PTCL was associated with inferior overall survival compared with PTCL without TP63 translocations (median survival: 17.9 months vs. 33.4 months, respectively; p<0.05). The clinical significance of the presence of a variant (non-TBL1XR1) partner is not known. Immunohistochemical staining for p63 protein with the 4A4 clone can be seen in cases without TP63 translocations, did not demonstrate prognostic significance in 1 study, and should not be considered a surrogate for TP63 translocation testing. TP63 translocations also have been identified in some B-cell non-Hodgkin lymphomas. Thus, the presence of a TP63 translocation should not be considered diagnostic for PTCL, and this result should be interpreted in the context of other pathologic, immunophenotypic, genetic, and clinical data. The clinical utility of TP63 testing in B-cell lymphomas has not been established.

**Useful For:** Supporting the diagnosis of peripheral T-cell lymphoma when coordinated with a consultation by anatomic pathology

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff of the TP63 probe sets. Among peripheral T-cell lymphomas, translocations involving TP63 have been associated with aggressive clinical behavior. B-cell lymphomas also may demonstrate this finding. Clinical and pathologic correlation is recommended.

**Reference Values:**
An interpretive report will be provided.

Pernicious Anemia Cascade

Clinical Information: Vitamin B12 deficiency can be caused by many factors, one of which is pernicious anemia, a condition resulting in deficient production of intrinsic factor in the parietal cells of the stomach. Intrinsic factor is a protein that is needed to assist in the absorption of vitamin B12 into the small intestine. Vitamin B12 is converted into adenosylcobalamin, which converts L-methylmalonic acid to succinyl coenzyme A; hence, a decrease in vitamin B12 absorption in the intestine can cause an excess of methylmalonic acid within the body. Vitamin B12 deficiency may present with any combination of the following: macrocytic anemia, glossitis (painful inflammation of the tongue), peripheral neuropathy, weakness, hyperreflexia, ataxia, loss of proprioception, poor coordination, and affective behavioral changes. These manifestations may occur in any combination; many patients present with neurologic symptoms without macrocytic anemia. A group of tests is often required to establish the correct diagnosis as determination of vitamin B12 in serum does not detect all cases of vitamin B12 deficiency. Mayo Clinic's Department of Laboratory Medicine and Pathology offers a diagnostic algorithm to expedite the identification of patients with vitamin B12 deficiency. This algorithm takes into account the following facts: -The most sensitive test for vitamin B12 deficiency at the cellular level is the assay for methylmalonic acid (MMA). -Nearly half of the cases of pernicious anemia can be unambiguously identified if the serum test for intrinsic factor blocking antibody is positive (this is a simpler and less expensive test than the MMA). -Serum gastrin is usually markedly increased in pernicious anemia (as a result of gastric atrophy) and this test can be used as a substitute for the more complicated and more expensive Schilling test of intestinal absorption of vitamin B12. The algorithm is similar to that published by Green,(1) except that the serum gastrin assay is performed in place of the Schilling test. Experience with both Mayo Clinic and Mayo Medical Laboratories’ cases has corroborated that this is a cost-effective alternative to the Schilling test. In our experience, >90% of laboratory test costs can be saved by using the algorithm rather than ordering all of the services for a patient suspected of having B12 deficiency. Furthermore, the substitution of the serum gastrin assay for the Schilling test offers 3 advantages: 1. It is an in vitro test that does not require administration of radioisotopes to patients 2. It can be performed on mailed-in specimens 3. It is much less expensive Only those tests that are appropriate, as defined by the algorithm, will be performed.

Useful For: Diagnosis of pernicious anemia Diagnosis of vitamin B12 deficiency-associated neuropathy

Interpretation: Vitamin B12 >400 ng/L Results do not suggest B12 deficiency-no further testing. Vitamin B12 150 to 400 ng/L Borderline vitamin B12 level-methylmalonic acid (MMA) is performed. If MMA is >0.40 nmol/mL, then intrinsic factor blocking antibody (IFBA) is performed. Vitamin B12 <150 ng/L Vitamin B12 deficiency-IFBA is performed. If IFBA is negative or indeterminate, then gastrin is performed. MMA < or =0.40 nmol/mL This value implies that there is no vitamin B12 deficiency at the cellular level. IFBA positive Consistent with pernicious anemia, Graves disease, or Hashimoto thyroiditis. Gastrin >200 pg/mL Result consistent with pernicious anemia. Gastrin <200 pg/mL Result does not suggest pernicious anemia. See Vitamin B12 Deficiency Evaluation in Special Instructions.

Reference Values: 180-914 ng/L


Peroxosomal Disorder Panel by Next-Generation Sequencing

Clinical Information: Peroxisomes are responsible for catabolic actions of cells, including beta oxidation of very long chain fatty acids, and anabolic actions, including biosynthesis of bile acids and plasmalogens. Peroxisomal disorders can be categorized into 2 major groups based on the function that is disrupted: peroxisomal biogenesis disorders and single peroxisomal enzyme deficiencies. Peroxisomal biogenesis disorders are caused by defective assembly of the organelle resulting in some amount of deficient functional peroxisomes. Severity of disease is dependent on amount of remaining
functional peroxisomes. Peroxisomal biogenesis disorders include the Zellweger spectrum: Zellweger syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease. Clinical features include developmental delay, liver disease, blindness, and deafness, and are usually progressive. Severity is variable with Zellweger syndrome being most severe and infantile Refsum disease being least severe. These are due to mutations in the PEX genes that are responsible for encoding proteins for peroxisome assembly. Peroxisomal enzyme deficiencies cause a disruption in peroxisomal function, although the organelles remain intact. The most common peroxisomal disorder, X-linked adrenoleukodystrophy, is an enzyme deficiency due to mutations in the ABCD1 gene. Other enzyme deficiencies include rhizomelic chondrodysplasia type 2 and 3, and congenital bile acid synthesis defect. Preliminary biochemical testing may be helpful in making a diagnosis. Recommended first-tier biochemical testing for peroxisomal disorders analyzes very long chain fatty acids is POX / Fatty Acid Profile, Peroxisomal [C22-C26], Serum. This panel includes sequencing of 30 genes related to both peroxisomal biogenesis disorders and enzyme deficiencies. See table below for additional information. Gene Disease Name/Locus Name OMIM ID Inheritance ABCD1 X-linked adrenoleukodystrophy 300100 XL ABCD2 Adrenoleukodystrophy-like/ related 601081 XL ABCD3 Congenital bile acid synthesis defect-5 603402 NA ACOX1 Acyl-CoA oxidase deficiency 264470 AR AR ACOX3 None at present time 603402 NA AGPS Rhizomelic chondrodysplasia punctate, type 3 (RCDP) 600121 AR AMACR Alpha-methylacyl-CoA racemase deficiency; bile acid synthesis defect, congenital, 614307, 214950 AR CAT Acatalasemia 614097 AR DNM1L Encephalopathy, lethal, due to defective mitochondrial and peroxisomal fission 614388 AD ECH1 None at present time 600696 NA GNPAT Rhizomelic chondrodysplasia punctata, type 2 (RCDP) 222765 AR HSD17B4 D-bifunctional enzyme deficiency; Perretta syndrome 261515, 233400 AR PEX1 Zellweger; peroxisome biogenesis disorder 214100 AR PEX10 Zellweger; peroxisome biogenesis disorder 614871 AR PEX11B Zellweger; peroxisome biogenesis disorder 614920 AR PEX12 Zellweger; peroxisome biogenesis disorder 614859, 266510 AR PEX13 Zellweger; peroxisome biogenesis disorder 614885, 614883 AR PEX14 Zellweger; peroxisome biogenesis disorder 614887 AR PEX16 Zellweger; peroxisome biogenesis disorder 614877, 614876 AR PEX19 Zellweger; peroxisome biogenesis disorder 614886 AR PEX2 Zellweger; peroxisome biogenesis disorder 614867, 614866 AR PEX26 Zellweger; peroxisome biogenesis disorder 614872, 614873 AR PEX3 Zellweger; peroxisome biogenesis disorder 614882 AR PEX5 Zellweger; peroxisome biogenesis disorder 614877, 614876 AR PEX6 Zellweger; peroxisome biogenesis disorder 614863, 614862 AR PEX7 Rhizomelic chondrodysplasia punctate, type 1 (RCDP) 215100, 614879 AR PHYH Refsum disease 266500 AR SCP2 Leukoencephalopathy with dystonia and motor neuropathy 613724 AR SUGCT Glutaric aciduria III 231690 AR TRIM37 Mulibrey nanism 253250 AR AR=autosomal recessive AD=autosomal dominant

**Useful For:** Follow up of abnormal biochemical result, usually very long chain fatty acid test consistent with peroxisomal disorder Identifying mutations within genes known to be associated with peroxisomal disorders, allowing for predictive testing of at-risk family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:** An interpretive report will be provided.

Perphenazine, (Trilafon), Serum

Reference Values:
Reference Range: 5.0 - 30.0 ng/mL

Low-dose therapeutic range for Perphenazine: 0.5 - 2.5 ng/mL

Persimmon, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


pH, 24 Hour, Urine

Clinical Information: Urine pH is a measure of the acidity/alkalinity of urine and by itself usually
provides little useful information. Under normal conditions its value is influenced by the type of diet. Some diets (eg, diets rich in meat) have more acid content than others (eg, vegetarian diets). Changes in urine pH may reflect systemic acid-base disorders. For example, the normal response during metabolic acidosis is a lowering of the urine pH to <5. If the pH is >5, then a defect in urine acidification should be considered. A urine pH >7 is suggestive of infection by a urea-splitting organism such as Proteus mirabilis. Therapeutic interventions to either alkalize or acidify the urine are necessary for some diseases. For example, some crystals have a propensity to form in alkaline urine, while others form in relative acidic urine, and changing the pH may reduce stone formation.

Useful For: Assessment of patients with metabolic acidosis Assessment of crystalluria Monitoring the effectiveness of alkalinization or acidification of urine for certain medical conditions (eg, treatment of uric acid nephrolithiasis)

Interpretation: Dependent on clinical condition A pH >7 suggests the presence of urinary tract infection with a urea-splitting organism.

Reference Values: 4.5-8.0

**UPHB** 9572

**pH, Body Fluid**

Clinical Information: The pH value is a measure of hydrogen ion concentration. A variety of disease processes can alter pH values. Determining the pH value of a body fluid may help characterize the nature of the fluid.

Useful For: Gastric fluid pH can help determine if acid production in the stomach is normal.

Interpretation: Normal gastric fluid has a pH <3.5; any higher pH is abnormal.

Reference Values: Varies with fluid type and location.


**FPHFL** 57309

**pH, Fecal**

Reference Values: 5.0 - 8.5

**PHU** 9312

**pH, Urine**

Clinical Information: Urine pH is a measure of the acidity/alkalinity of urine, and by itself usually provides little useful information. Under normal conditions its value is influenced by the type of diet (some diets: eg, diets rich in meat-having more acid content than others; eg, vegetarian diets). Assessment of urine pH may be useful in the evaluation of systemic acid-base disorder. For example, the normal response during metabolic acidosis is a lowering of the urine pH to less than 5. If it is >5, then a defect in urine acidification should be considered. Often a urine pH above 7 is suggestive of infection of a urea splitting organism such as proteus mirabilis. Monitoring of urine pH may also be helpful during therapeutic interventions to either alkalize the urine (such as for treatment of uric acid nephrolithiasis) or acidify the urine. Finally, when assessing crystalluria, noting the urine pH may be helpful since some crystals have a propensity to form in alkaline urine while others form in relative acidic urine.

Useful For: Assessment of patients with metabolic acidosis Assessment of crystalluria Monitoring the effectiveness of alkalinization or acidification of urine for certain medical conditions (eg, treatment of uric acid nephrolithiasis)
Interpretation: Dependent on clinical condition.

Reference Values:
N/A

**FPHAS**  
57580

**Phadiatop (Allergy Screen)**

Reference Values: Negative

The Phadia Phadiatop test is an allergy screening test with excellent sensitivity and specificity for inhalant allergy. It uses an ImmunoCAP with a balanced mixture of representative allergens, including grasses, trees, weeds, cat, dog, mites and molds. A positive result indicates that the patient is allergic to one or more of these allergens; a negative indicates the patient is not allergic to inhalant allergens. Note that the test does not assess a patient’s sensitivity to food, drug, chemical or certain unusual or rare allergens.

**PHAGP**  
65665

**Phagocytic Primary Immunodeficiency (PID) Gene Panel**

Clinical Information: Primary immunodeficiencies (PID) that affect the function of phagocytes (neutrophils, monocytes, macrophages, and eosinophils) predispose patients to a narrow spectrum of specific infections as a result of impaired killing of bacteria and fungi. Chronic granulomatous disease (CGD), due to impaired production of reactive oxygen intermediates, is characterized by infections (ie, Staphylococcus aureus, Burkholderia cepacia complex, Serratia marcescens, Nocardia, and Aspergillus sp.) that involve the skin, lungs, lymph nodes, liver, and bones, although any organ or tissue can be affected. Patients may also experience immune dysregulation, resulting in granuloma formation, colitis, and other inflammatory disorders. While most affected individuals are diagnosed prior to 5 years of age, patients may present into late adulthood. Tests that measure neutrophil superoxide production by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, including the dihydrorhodamine (DHR) or nitroblue tetrazolium (NBT) tests, may be used in establishing a diagnosis. X-linked CGD, the most common form, is caused by pathogenic variants in CYBB. In some cases, a contiguous gene deletion may result in CGD along with McLeod neuroacanthocytosis syndrome. In cases of a large contiguous gene deletion, patients may also inherit RPGR-related retinitis pigmentosa, Duchenne muscular dystrophy, and ornithine transcarbamylase deficiency. A chromosomal microarray may be indicated if a contiguous gene deletion is suspected. In addition to the X-linked form, CGD may also be inherited in an autosomal recessive pattern, due to biallelic pathogenic variants in the other genes that encode the remainder of the subunits of phagocyte NADPH, including CYBA, NCF1, NCF2, and NCF4 (Note: NCF1 is not currently included on this panel). Similarly to CGD, complete glucose 6-phosphate dehydrogenase (G6PD) deficiency can result in an increased susceptibility to infection due to impaired neutrophil respiratory burst. G6PD deficiency is also inherited in an X-linked pattern due to pathogenic variants in G6PD. Chronic nonspherocytic hemolytic anemia occurs in severe deficiency, while acute hemolytic episodes (typically triggered by some medications, ingestion of fava beans, viral or bacterial infections, etc) are observed in less severe G6PD deficiency. Patients with myeloperoxidase deficiency also show a reduced ability of the neutrophil to generate a respiratory burst, as evidenced by abnormal DHR results, but show normal superoxide production levels and NBT staining. Neutrophils contain azurophilic (or primary) granules, specific (or secondary) granules, and tertiary granules that contain antimicrobial substances. Azurophilic granules contain myeloperoxidase, bactericidal/permeability-increasing protein, defensins, neutrophil elastase, and cathepsin G. Specific granules contain lactoferrin, lysozyme, NADPH oxidase, alkaline phosphatase, collagenase, histaminase, and cathelicidin. Tertiary granules contain cathepsin, gelatinase, and collagenase. Deficiency of myeloperoxidase can occur as an autosomal recessive condition due to variants in myeloperoxidase (MPO) and results in a susceptibility to Candida infections. Papillon-Lefèvre Syndrome (PALS) is an autosomal recessive disorder due to pathogenic variants in CTSC (lysosomal cysteine protease cathepsin C, also known as dipeptidyl peptidase I [DPP1]). DPP1 is necessary for posttranslational modification of the serine proteases in the neutrophil azurophilic granules, activation of granzymes A and B of cytotoxic lymphocytes, and activation of mast cell chymases. PALS typically...
presents with severe periodontal disease and keratosis palmoplantaris, along with mild immunodeficiency. In specific granule deficiency (SGD), neutrophils lack expression of secondary and tertiary granule proteins, have an atypical bilobed nuclear morphology, and demonstrate defects in chemotaxis and bactericidal activity. SGD is due to pathogenic variants in CEBPE, which is a myeloid-specific transcription factor. Leukocyte adhesion deficiencies (LAD) are characterized by recurrent bacterial infections due to reduced ability of neutrophils to adhere to various substances and migrate to sites of infection, as well as defective phagocytic and respiratory burst response to bacteria and yeast. Patients often are first noticed due to omphalitis, but later gingivitis/periodontitis, pneumonia, peritonitis, and deep abscesses may develop. LAD can be caused by pathogenic variants in ITGB2, which encodes for the CD18 antigen (LAD1); and SLC35C1, which encodes for a GDP-fucose transporter (LAD2) (Note: SLC35C1 is not currently included on this panel) or FERMT3 (LAD3). Although the neutrophil functional studies are similar between LAD1 and LAD2, the clinical course in LAD2 is milder, though patients may also present with other features (ie, mental and growth retardation) due to abnormal fucose metabolism. LAD3 presents similarly to LAD1, but platelets are also affected resulting in clotting defects. Pathogenic variants in RASGRP2 (also inherited in a recessive pattern) mimic the phenotype of LAD3. Recessively inherited defects in PMM2 (congenital disorder of glycosylation type IA) show diminished neutrophil chemotaxis resulting in severe infections. Granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulates the formation of colonies of neutrophils and macrophages from bone marrow precursors, but is also required for proper neutrophil function. Recessive inheritance of pathogenic variants in CSF2RA, which encodes for the alpha chain of the GM-CSF receptor, disrupts GM-CSF signaling and results in defects in neutrophil adhesion, phagocytosis, superoxide formation, and microbial killing. Clinically, this manifests as pulmonary alveolar proteinosis and increased susceptibility to infections (pulmonary and extrapulmonary). The fMet-Leu-Phe receptor, encoded by FPR1, is located on the cell surface and is involved in chemotaxis phagocytic cells. Variants in FPR1 may present with aggressive periodontitis and FPR1 governs neutrophil function during acute inflammation. Netherton syndrome (NS), due to pathogenic variants in SPINK5 encoding LEKTI (lymphoepithelial Kazal-type-related inhibitor), is characterized by extensive skin inflammation, hair abnormalities, atopic manifestations, and recurrent bacterial infections. Although various immunologic defects have been suggested to contribute to the immune deficiency, in some cases NK cells demonstrate an immature phenotype with impaired degranulation and cytotoxic effects. Patients may also have decreased circulating B-cells and elevated IgE and IgA.

Table 1. Genes included in the Phagocytic / Chronic Granulomatous Disease PID Gene Panel

<table>
<thead>
<tr>
<th>GENE SYMBOL (ALIAS)</th>
<th>PROTEIN OMIM INHERITANCE PHENOTYPE DISORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEBPE CCAAT/enhancer-binding protein epsilon</td>
<td>600749 AR Specific granule deficiency</td>
</tr>
<tr>
<td>CSF2RA Granulocyte-macrophage colony-stimulating factor receptor subunit alpha isoform</td>
<td>306250 XL Pulmonary surfactant metabolism dysfunction</td>
</tr>
<tr>
<td>CTSC Dipeptidyl peptidase</td>
<td>602365 AR Haim-Munk syndrome, Papillon-Lefevre syndrome, Periodontitis 1, juvenile CYBA Cytochrome b-245 light chain</td>
</tr>
<tr>
<td>CYBA Cytochrome b-245 light chain</td>
<td>300481 XL Chronic granulomatous disease</td>
</tr>
<tr>
<td>CYBB Cytochrome b-245 heavy chain</td>
<td>607901 AR Leukocyte adhesion deficiency, type III</td>
</tr>
<tr>
<td>FPR1 fMet-Leu-Phe receptor</td>
<td>136537 AR Juvenile periodontitis G6PD Glucose-6-phosphate 1-dehydrogenase isoform b 305900 XL Hemolytic anemia, chronic granulomatous disease ITGB2 Integrin beta-2 precursor 600065 AR Leukocyte adhesion deficiency type 1</td>
</tr>
<tr>
<td>MPO Myeloperoxidase precursor</td>
<td>606989 AR Myeloperoxidase deficiency</td>
</tr>
<tr>
<td>NCF2 Neutrophil cytosol factor 2 isoform 1</td>
<td>608515 AR Chronic granulomatous disease</td>
</tr>
<tr>
<td>NCF4 Neutrophil cytosol factor 4 isoform 2</td>
<td>601488 AR Chronic granulomatous disease</td>
</tr>
<tr>
<td>PMM2 (CDG1) Phosphomannomutase 2</td>
<td>601785 AR Congenital disorder of glycosylation, type Ia</td>
</tr>
<tr>
<td>RASGRP2 RAS guanyl-releasing protein 2 isoform a</td>
<td>605577 AR Bleeding disorder, platelet-type, 18, LAD-III</td>
</tr>
<tr>
<td>SPINK5 Serine protease inhibitor Kazal-type 5 isoform b preproprotein</td>
<td>605010 AD/AR Atoxyl(AD), Netherton syndrome (AR) AD=autosomal dominant AR=autosomal recessive XL=X-linked</td>
</tr>
</tbody>
</table>

**Useful For:** Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of primary immunodeficiency due to phagocytic defects, chronic granulomatous disease, or related disorders Establishing a diagnosis and, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying variants within genes known to be associated primary immunodeficiency due to phagocytic defects, chronic granulomatous disease, or related disorders allowing for predictive testing of at-risk family members.
**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Phencyclidine (PCP) Confirmation, Chain of Custody, Meconium**

**Clinical Information:** Phencyclidine (PCP) was originally developed as an anesthetic in the 1950s but later was abandoned because of a high frequency of postoperative delirium with hallucinations. It was classed as a dissociative anesthetic because, in the anesthetized state, the patient remains conscious with staring gaze, flat facies, and rigid muscles.(1) PCP binds with high affinity to sites located in the cortex and limbic structures, resulting in blocking of N-methyl-D-aspartate (NMDA)-type glutamate receptors.(1) PCP became a drug of abuse in the 1970s because of its hallucinogenic effects.(1,2) PCP is approximately 65% protein bound and has a volume of distribution (Vd) of 5.3 to 7.5 L/kg. The drug is metabolized by the liver via oxidative hydroxylation and has a dose-dependent half-life ranging from 7 to 46 hours.(2) Meconium is the first fecal material passed by the neonate. Meconium forms in the first trimester of pregnancy but is seldom excreted before the 34th week. It is composed of approximately 70% water, bile acids, cholesterol, squamous cells, protein and drug metabolites, and no bacteria are normally present. Prebirth excretion of meconium is a sign of fetal distress. Because drugs and metabolites can accumulate in meconium, assessment of meconium for the presence of illicit drugs can be an indicator of maternal drug use during pregnancy. Illicit drug use during pregnancy can have a profound effect on fetal development. The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid.(3) The first evidence of meconium in the fetal intestine appears at approximately the 10th to 12th week of gestation,
and slowly moves into the colon by the 16th week of gestation.(4) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(3) Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection of in utero drug exposure up to 5 months before birth. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. Since the evidence of illicit drug use during pregnancy can be cause for separating the baby from the mother, a complete chain of custody ensures that the test results are appropriate for legal proceedings.

**Interpretation:** The presence of phencyclidine in meconium is indicative of in utero drug exposure up to 5 months before birth.

**Reference Values:**
- **Negative**
  - Positives are reported with a quantitative LC-MS/MS result.
- **Cutoff concentrations**
  - PCP by LC-MS/MS: 10 ng/g

**Clinical References:**

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**Phencyclidine (PCP) Confirmation, Meconium**

**Clinical Information:** Phencyclidine (PCP) was originally developed as an anesthetic in the 1950s but later was abandoned because of a high frequency of postoperative delirium with hallucinations. It was classed as a dissociative anesthetic because, in the anesthetized state, the patient remains conscious with staring gaze, flat facies, and rigid muscles.(1) PCP binds with high affinity to sites located in the cortex and limbic structures, resulting in blocking of N-methyl-D-aspartate (NMDA)-type glutamate receptors.(1) PCP became a drug of abuse in the 1970s because of its hallucinogenic effects.(1,2) PCP is approximately 65% protein bound and has a volume of distribution (Vd) of 5.3 to 7.5 L/kg. The drug is metabolized by the liver via oxidative hydroxylation and has a dose-dependent half-life ranging from 7 to 46 hours.(2) Meconium is the first fecal material passed by the neonate. Meconium forms in the first trimester of pregnancy but is seldom excreted before the 34th week. It is composed of approximately 70% water, bile acids, cholesterol, squamous cells, protein and drug metabolites, and no bacteria are normally present. Prebirth excretion of meconium is a sign of fetal distress. Because drugs and metabolites can accumulate in meconium, assessment of meconium for the presence of illicit drugs can be an indicator of maternal drug use during pregnancy. Illicit drug use during pregnancy can have a profound effect on fetal development. The disposition of drug in meconium is not well understood. The proposed mechanism is that the fetus excretes drug into bile and amniotic fluid. Drug accumulates in meconium either by direct deposit from bile or through swallowing of amniotic fluid.(3) The first evidence of meconium in the fetal intestine appears at approximately the tenth to twelfth week of gestation, and slowly moves into the colon by the sixteenth week of gestation.(4) Therefore, the presence of drugs in meconium has been proposed to be indicative of in utero drug exposure during the final 4 to 5 months of pregnancy, a longer historical measure than is possible by urinalysis.(3)

**Useful For:** Detection of in utero to phencyclidine (PCP) exposure up to 5 months before birth.
**Interpretation:** The presence of phencyclidine (PCP) in meconium is indicative of in utero drug exposure up to 5 months before birth.

**Reference Values:**
- Negative
- Positives are reported with a quantitative LC-MS/MS result.
- Cutoff concentrations
  - PCP by LC-MS/MS: 10 ng/g

**Clinical References:**

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**PCPUG 9788**

**Phencyclidine (PCP), Confirmation, serum**

**Reference Values:**
- Toxic: Greater than 100 ng/mL
- Serious Toxicities likely: Greater than 300 ng/mL

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**PCPX 62739**

**Phencyclidine Confirmation, Chain of Custody, Urine**

**Clinical Information:** Phencyclidine (PCP) is a drug of abuse. This compound affects diverse neural pathways and interacts with cholinergic, adrenergic, GABA-secreting, serotonergic, opiate neuronal receptors, and gamma receptors. It has analgesic, anesthetic, and stimulatory effects, giving bizarre behavior, ranging from depression through catatonia, euphoria, violent rage, and hallucinations. Most fatalities result from its hypertensive effect. Diagnosis of PCP usage depends on drug screen. PCP is excreted in the urine. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detection of drug abuse involving phencyclidine (angel dust or angel hair). Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** The presence of phencyclidine (PCP) in urine at concentrations >10 ng/mL is a strong indicator that the patient has used PCP.

**Reference Values:**
- Negative
- Cutoff concentrations
  - IMMUNOASSAY SCREEN
    - <25 ng/mL
  - Phencyclidine by GC-MS: <10 ng/mL

**Clinical References:**
3. Bayorh MA, Zokowska-Grojec A, Palkovits M,
Phencyclidine Confirmation, Urine

Clinical Information: Phencyclidine (PCP) is a drug of abuse. This compound affects diverse neural pathways and interacts with cholinergic, adrenergic, GABA-secreting, serotoninergic, opiate neuronal receptors, and gamma receptors. It has analgesic, anesthetic, and stimulatory effects, giving bizarre behavior, ranging from depression through catatonia, euphoria, violent rage, and hallucinations. Most fatalities result from its hypertensive effect. PCP is excreted in the urine.

Useful For: Detection of drug abuse involving phencyclidine (angel dust or angel hair)

Interpretation: The presence of phencyclidine (PCP) in urine at concentrations >10 ng/mL is a strong indicator that the patient has used PCP.

Reference Values:
Negative
Cutoff concentrations
Phencyclidine by GC-MS: <10 ng/mL


Phenobarbital, Serum

Clinical Information: Phenobarbital is a general central nervous system (CNS) suppressant that has proven effective in the control of generalized and partial seizures. It is frequently coadministered with phenytoin for control of complex seizure disorders and with valproic acid for complex parietal seizures. Phenobarbital is administered in doses of 60 to 300 mg/day in adults or 3 to 6 mg/kg/day in children. Phenobarbital is slowly but completely absorbed, with bioavailability in the range of 100%. It is approximately 50% protein bound with a volume of distribution of 0.5 L/kg. Phenobarbital has a long half-life of 96 hours, with no known active metabolites. Sedation is common at therapeutic concentrations for the first 2 to 3 weeks of therapy, but this side effect disappears with time. Toxicity due to phenobarbital overdose is characterized by CNS sedation and reduced respiratory function. Mild symptoms characterized by ataxia, nystagmus, fatigue, or attention loss, occur at blood concentrations above 40.0 mcg/mL. Symptoms become severe at concentrations of 60.0 mcg/mL and higher. Toxicity becomes life-threatening at concentrations over 100.0 mcg/mL. Death usually occurs due to respiratory arrest when pulmonary support is not supplied manually. There are no known drug interactions that significantly affect the pharmacokinetics of phenobarbital; conversely, phenobarbital affects the pharmacokinetics of other drugs significantly because it induces the synthesis of enzymes associated with the hepatic cytochrome P450 metabolic pathway. Acute intermittent porphyria attacks may be induced by phenobarbital stimulation of hepatic cytochrome P450.

Useful For: Monitoring for appropriate therapeutic concentration of phenobarbital Assessing compliance or toxicity

Interpretation: Clinical response to the drug correlates strongly with blood concentration. Dosage adjustments are made after 2 weeks of therapy to achieve steady-state blood levels in the range of 20.0 to 40.0 mcg/mL for adults; 15.0 to 30.0 mcg/mL for infants and children. Patients chronically administered phenobarbital usually do not experience sedation unless the blood concentration is above 40.0 mcg/mL.

Reference Values:
Therapeutic: 10.0-40.0 mcg/mL
Critical value: > or =60.0 mcg/mL


Phenosense Combination HIV Drug Resistance Assay
Reference Values:
A final report will be attached in MayoAccess.

Phenosense Entry HIV Drug Resistance Assay
Reference Values:
A final report will be attached in MayoAccess.

Phenosense HIV Drug Resistance Replication Capacity
Reference Values:
A final report will be attached in MayoAccess.

Phenylalanine and Tyrosine, Blood Spot
Clinical Information: Phenylketonuria (PKU) is the most frequent inherited disorder of amino acid metabolism (about 1:10,000-1:15,000) and was the first successfully treated inborn error of metabolism. It is inherited in an autosomal recessive manner and is caused by a defect in the enzyme phenylalanine hydroxylase (PAH), which converts the essential amino acid phenylalanine to tyrosine. Deficiency of PAH results in decreased levels of tyrosine and an accumulation of phenylalanine in blood and tissues. Untreated, PKU leads to severe brain damage with intellectual impairment, behavior abnormalities, seizures, and spasticity. The level of enzyme activity differentiates classic PKU (PAH activity <1%) from other milder forms; however, all are characterized by increased levels of phenylalanine (hyperphenylalaninemia). Treatment includes the early introduction of a diet low in phenylalanine. Tetrahydrobiopterin (BH4) is a cofactor of not only PAH, but also of the tyrosine and tryptophan hydroxylases. Approximately 2% of patients with hyperphenylalaninemia have a deficiency of BH4, which causes a secondary deficit of the neurotransmitters dopamine and serotonin. There are 4 autosomal-recessive disorders associated with BH4 deficiency plus hyperphenylalaninemia; guanosine triphosphate cyclohydrolase deficiency, 6-pyruvoyl tetrahydropterine synthase deficiency, dihydropteridine reductase deficiency, and pterin-4 alpha carbinolamine dehydratase (PCD) deficiency. This group of disorders, with the exception of PCD, is characterized by progressive dystonia, truncal hypotonia, extreme hypertonia, seizures, and mental retardation though milder presentations exist. PCD has no symptoms other than transient alterations in tone. Treatment may include administration of BH4, L-dopa (and carbidopa) 5-hydroxytryptophan supplements, and a low phenylalanine diet. Tyrosine is a nonessential amino acid that derives from dietary sources, the hydroxylation of phenylalanine, or protein breakdown. Primary (PKU) and secondary (defects of BH4 metabolism) hyperphenylalaninemia can cause abnormally low levels of tyrosine. Measurement of the phenylalanine:tyrosine ratio is helpful in monitoring appropriate dietary intake.

Useful For: Monitoring effectiveness of dietary therapy in patients with hyperphenylalaninemia

Interpretation: The quantitative results of phenylalanine and tyrosine with age-dependent reference values are reported without added interpretation. When applicable, reports of abnormal results may contain an interpretation based on available clinical information. A phenylalanine:tyrosine ratio higher than 3 is considered abnormal.

Reference Values: PHENYLALANINE

PKU

Phenylalanine and Tyrosine, Plasma

Clinical Information: Phenylketonuria (PKU) is the most frequent inherited disorder of amino acid metabolism (about 1:10,000-1:15,000) and was the first successfully treated inborn error of metabolism. It is inherited in an autosomal recessive manner and is caused by a defect in the enzyme phenylalanine hydroxylase (PAH), which converts the essential amino acid phenylalanine to tyrosine. Deficiency of PAH results in decreased levels of tyrosine and an accumulation of phenylalanine in blood and tissues. Untreated, PKU leads to severe brain damage with intellectual impairment, behavior abnormalities, seizures, and spasticity. The level of enzyme activity differentiates classic PKU (PAH activity <1%) from other milder forms; however, all are characterized by increased levels of phenylalanine (hyperphenylalaninemia). Treatment includes the early introduction of a diet low in phenylalanine. Tetrahydrobiopterin (BH4) is a cofactor of not only PAH, but also of the tyrosine and tryptophan hydroxylases. Approximately 2% of patients with hyperphenylalaninemia have a deficiency of BH4, which causes a secondary deficit of the neurotransmitters dopamine and serotonin. There are 4 autosomal-recessive disorders associated with BH4 deficiency plus hyperphenylalaninemia; guanosine triphosphate cyclohydrolase deficiency, 6-pyruvoyl tetrahydropterine synthase deficiency, dihydropteridine reductase deficiency, and pterin-4 alpha carbinolamine dehydratase (PCD) deficiency. This group of disorders, with the exception of PCD, is characterized by progressive dystonia, truncal hypotonia, extreme hypertonia, seizures, and mental retardation though milder presentations exist. PCD has no symptoms other than transient alterations in tone. Treatment may include administration of BH4, L-dopa (and carbidopa) 5-hydroxytryptophan supplements, and a low phenylalanine diet. Tyrosine is a nonessential amino acid that derives from dietary sources, the hydroxylation of phenylalanine, or protein breakdown. Primary (PKU) and secondary (defects of BH4 metabolism) hyperphenylalaninemia can cause abnormally low levels of tyrosine. Measurement of the phenylalanine:tyrosine ratio is helpful in monitoring appropriate dietary intake.

Useful For: Monitoring effectiveness of dietary therapy in patients with hyperphenylalaninemia

Interpretation: The quantitative results of phenylalanine and tyrosine with age-dependent reference values are reported without added interpretation. When applicable, reports of abnormal results may contain an interpretation based on available clinical interpretation. A phenylalanine:tyrosine ratio higher than 3 is considered abnormal.

Reference Values:

PHENYLALANINE
  Premature: 98-213 nmol/mL
  0-31 days: 38-137 nmol/mL
  1-24 months: 31-75 nmol/mL
  2-18 years: 26-91 nmol/mL
  > or =19 years: 35-85 nmol/mL

TYROSINE
  29-149 nmol/mL

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Convension Formulas:
Result in mg/dL x 60.6 = result in nmol/mL

TYROSINE
Premature: 147-420 nmol/mL
0-31 days: 55-147 nmol/mL
1-24 months: 22-108 nmol/mL
2-18 years: 24-115 nmol/mL
> or =19 years: 34-112 nmol/mL

Convension Formulas:
Result in mg/dL x 55.6 = result in nmol/mL
Result in nmol/mL x 0.0181 = result in mg/dL

Clinical References:

Phenytoin, Free, Serum

Clinical Information: Phenytoin is the drug of choice to treat and prevent tonic-clonic and psychomotor seizures. If phenytoin alone will not prevent seizure activity, coadministration with phenobarbital is usually effective. Phenytoin is highly protein-bound (90%), mostly to albumin. Ten percent of the phenytoin circulates in the free, unbound form. Free phenytoin is the active form of the drug, available to cross biologic membranes and bind to receptors. Increased free phenytoin produces an enhanced pharmacologic effect. At the same time, the free fraction is more available to the liver to be metabolized, so it is cleared more quickly. Concurrent use of phenytoin and valproic acid (another frequently used antiepileptic) may result in altered valproic acid levels and/or altered phenytoin levels. Due to the complex situation involving displacement of protein-bound phenytoin and inhibition of phenytoin metabolism, as well as the potential for decreased valproic acid concentrations, patients should be monitored for both phenytoin toxicity and therapeutic efficacy. Free phenytoin levels should be measured to provide the most accurate assessment of phenytoin activity early in therapy. At steady-state, free phenytoin and free valproic acid concentrations should be normalized. In renal failure, the opportunity for the free phenytoin fraction to be cleared is significantly reduced. The end result is that both the total and free concentration of phenytoin increase, with the free concentration increasing faster than the total. Dosage must be reduced to avoid toxicity. Accordingly, the free phenytoin level is the best indicator of adequate therapy in renal failure. Toxicity is a constant possibility because of the manner in which phenytoin is metabolized. Small increases in dose can lead to very large increases in blood concentration, resulting in early signs of toxicity such as nystagmus, ataxia, and dysarthria. Severe toxicity is typified by tremor, hyperreflexia, lethargy, and coma.

Useful For: Monitoring for appropriate therapeutic concentration of free phenytoin: free phenytoin level is the best indicator of adequate therapy in renal failure Assessing compliance and toxicity

Interpretation: Dose should be adjusted to achieve steady-state blood concentration of free phenytoin between 1.0 and 2.0 mcg/mL. The range for percent free phenytoin is 8% to 14%. Severe
toxicity occurs when the free phenytoin concentration is \( > 2.5 \text{ mcg/mL} \). However, response and side effects will be individual. 

**Reference Values:**
Therapeutic: 1.0-2.0 mcg/mL  Critical value: \( > 2.5 \text{ mcg/mL} \)

**Clinical References:** Richens A: Clinical pharmacokinetics of phenytoin. Clin Pharmacokinet 1979;4:153-169

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**Phenytoin, Total and Free, Serum**

**Clinical Information:** Phenytoin is the drug of choice to treat and prevent tonic-clonic and psychomotor seizures. If phenytoin alone will not prevent seizure activity, coadministration with phenobarbital is usually effective. Initial therapy with phenytoin is started at doses of 100 to 300 mg/day for adults or 4 mg/kg/day for children. Because absorption is variable and the drug exhibits zero-order (nonlinear) kinetics, dose must be adjusted within 5 days using blood concentration to guide therapy. Oral bioavailability ranges from 80% to 95% and is diet-dependent. Phenytoin exhibits zero-order pharmacokinetics; the rate of clearance of the drug is dependent upon the concentration of drug present. Therefore, phenytoin does not have a classical half-life like other drugs, since it varies with blood concentration. At a blood concentration of 15 mcg/mL, approximately half the drug in the patient's body will be eliminated in 20 hours. As the blood concentration drops, the rate at which phenytoin is excreted increases. Phenytoin has a volume of distribution of 0.65 L/kg, and is highly protein bound (90%), mostly to albumin. Phenytoin pharmacokinetics are significantly affected by a number of other drugs. Phenytoin and phenobarbital are frequently coadministered. Induction of the cytochrome P450 enzyme system by phenobarbital will increase the rate at which phenytoin is metabolized and cleared. At steady-state, enzyme induction will increase the rate of clearance of phenytoin such that the dose must be increased approximately 30% to maintain therapeutic levels. Uremia has a similar effect on phenytoin protein binding. In uremia, by-products of normal metabolism accumulate and bind to albumin, displacing phenytoin, which causes an increase in the free (active) fraction. Concurrent use of phenytoin and valproic acid (another frequently used antiepileptic) may result in altered valproic acid levels and/or altered phenytoin levels. Due to the complex situation involving displacement of protein-bound phenytoin and inhibition of phenytoin metabolism, as well as the potential for decreased valproic acid concentrations, patients should be monitored for both phenytoin toxicity and therapeutic efficacy. Free phenytoin levels should be measured to provide the most accurate assessment of phenytoin activity early in therapy. At steady-state, free phenytoin and free valproic acid concentrations should be normalized. The free phenytoin level is the best indicator of adequate therapy. In renal failure, the opportunity for the free phenytoin fraction to be cleared is significantly reduced. The end result is that both the total and free concentration of phenytoin increase, with the free concentration increasing faster than the total. Dosage must be reduced to avoid toxicity. Accordingly, the free phenytoin level is the best indicator of adequate therapy in renal failure. Toxicity is a constant possibility because of the manner in which phenytoin is metabolized. Small increases in dose can lead to very large increases in blood concentration, resulting in early signs of toxicity such as nystagmus, ataxia, and dysarthria. Severe toxicity is typified by tremor, hyperreflexia, lethargy, and coma. The outcome of phenytoin toxicity is not as serious as phenobarbital because phenytoin is not a central nervous system sedative.

**Useful For:** Monitoring for appropriate therapeutic concentration of both free and total phenytoin: free phenytoin level is the best indicator of adequate therapy in renal failure

**Interpretation:** Dose should be adjusted to achieve steady-state concentrations of total phenytoin between 10.0 and 20.0 mcg/mL, and free phenytoin between 1.0 and 2.0 mcg/mL. The range for percent free phenytoin is 8% to 14%. However, response and side effects will be individual. In patients with renal failure, total phenytoin is likely to be less than the therapeutic range of 10.0 to 20.0 mcg/mL. Severe toxicity occurs when the total blood concentration exceeds 30.0 mcg/mL.

**Reference Values:**
Phenytoin, Total
Therapeutic: 10.0-20.0 mcg/mL  Critical value: \( > 30.0 \text{ mcg/mL} \)
Phenytoin, Free
Therapeutic: 1.0-2.0 mcg/mL
Critical value: > or =2.5 mcg/mL


Phenytoin, Total and Phenobarbital Group, Serum

Clinical Information: Phenytoin, Total: Phenytoin is the drug of choice to treat and prevent tonic-clonic and psychomotor seizures. If phenytoin alone will not prevent seizure activity, coadministration with phenobarbital is usually effective. Initial therapy with phenytoin is started at doses of 100 to 300 mg/day for adults or 4 mg/kg/day for children. Because absorption is variable and the drug exhibits zero-order (nonlinear) kinetics, dose must be adjusted within 5 days using blood concentration to guide therapy. Oral bioavailability ranges from 80% to 95% and is diet-dependent. Phenytoin exhibits zero-order pharmacokinetics; the rate of clearance of the drug is dependent upon the concentration of drug present. Therefore, phenytoin does not have a classical half-life like other drugs, since it varies with blood concentration. At a blood concentration of 15 mcg/mL, approximately half the drug in the patient's body will be eliminated in 20 hours. As the blood concentration drops, the rate at which phenytoin is excreted increases. Phenytoin has a volume of distribution of 0.65 L/kg, and is highly protein bound (90%), mostly to albumin. Some drug side-effects occur in the therapeutic range; these include gingival hyperplasia, hyperglycemia, and skin rash. Phenytoin pharmacokinetics are significantly affected by a number of other drugs. As noted above, phenytoin and phenobarbital are frequently coadministered. Induction of the cytochrome P450 enzyme system by phenobarbital will increase the rate at which phenytoin is metabolized and cleared. At steady-state, enzyme induction will increase the rate of clearance of phenytoin such that the dose must be increased approximately 30% to maintain therapeutic levels. Uremia has a similar effect on phenytoin protein binding. In uremia, by-products of normal metabolism accumulate and bind to albumin, displacing phenytoin which causes an increase in the free fraction. Valproic acid, an antiepileptic frequently coadministered with phenytoin, competes for the same binding sites on albumin as phenytoin. Valproic acid displaces phenytoin from albumin, reducing the bound fraction and increasing the free fraction. The overall effect of coadministration of a therapeutic dose of valproic acid is that the total concentration of phenytoin decreases due to increased clearance but the free fraction increases; the free concentration of phenytoin, which is the active form remains virtually the same. Thus, no dosage adjustment is needed when valproic acid is added to maintain the same pharmacologic effect, but the total concentration of phenytoin decreases. In contrast to the valproic acid situation, in renal failure, there is not the same opportunity for the free phenytoin fraction to be cleared. The end result is that both the total and free concentration of phenytoin increase, with the free concentration increasing faster than the total. Dosage must be reduced to avoid toxicity. The free phenytoin level is the best indicator of adequate therapy in renal failure. Toxicity is a constant possibility because of the manner in which phenytoin is metabolized. Small increases in dose can lead to very large increases in blood concentration, resulting in early signs of toxicity such as nystagmus, ataxia, and dysarthria. Severe toxicity occurs when the blood concentration is >30 mcg/mL and is typified by tremor, hyperreflexia, and lethargy. The outcome of phenytoin toxicity is not as serious as phenobarbital because phenytoin is not a central nervous system sedative. Phenobarbital: Phenobarbital is a general central nervous system (CNS) suppressant that has proven effective in the control of generalized and partial seizures. It is frequently coadministered with phenytoin for control of complex seizure disorders and with valproic acid for complex parietal seizures. Phenobarbital is administered in doses of 60 to 300 mg/day in adults or 3 to 6 mg/kg/day in children. Phenobarbital is slowly but completely absorbed, with bioavailability in the range of 100%. It is approximately 50% protein bound with a volume of distribution of 0.5 L/kg. Phenobarbital has a long half-life of 96 hours, with no known active metabolites. Sedation is common at therapeutic concentrations for the first 2 to 3 weeks of therapy, but this side effect disappears with time. Toxicity due to phenobarbital overdose is characterized by CNS sedation and reduced respiratory function. Mild symptoms characterized by ataxia, nystagmus, fatigue, or attention loss, occur at blood concentrations...
>40 mcg/mL. Symptoms become severe at concentrations > or =60 mcg/mL. Toxicity becomes life-threatening at concentrations >100 mcg/mL. Death usually occurs due to respiratory arrest when pulmonary support is not supplied manually. There are no known drug interactions that significantly affect the pharmacokinetics of phenobarbital; conversely, phenobarbital affects the pharmacokinetics of other drugs significantly because it induces the synthesis of enzymes associated with the hepatic cytochrome P450 metabolic pathway. Acute intermittent porphyria attacks may be induced by phenobarbital stimulation of hepatic cytochrome P450.

**Useful For:** Monitoring for appropriate therapeutic concentration of phenytoin and phenobarbital
Assessing compliance or toxicity

**Interpretation:** The therapeutic ranges for adults taking phenytoin have been established at 10 to 20 mcg/mL for total phenytoin (bound plus unbound). The therapeutic range for phenobarbital is 10 to 40 mcg/mL. Within these ranges, most people will respond to the drugs without symptoms of toxicity. However, response and side effects will be individual. Dosage determinations and adjustments must be evaluated on a case-by-case basis. A free (unbound) phenytoin level may also need to be ordered when a person has kidney failure, liver disease, hypoalbuminemia, or is taking other medications like aspirin, naproxen, or ibuprofen, in which situation the percentage of free (active) phenytoin may be increased.

**Reference Values:**
PHENYTOIN, TOTAL
Therapeutic: 10.0-20.0 mcg/mL
Critical value: > or =30.0 mcg/mL

PHENOBARBITAL
Therapeutic: 10.0-40.0 mcg/mL:
Critical value: > or =60.0 mcg/mL


**Phenytoin, Total, Serum**

**Clinical Information:** Phenytoin is the drug of choice to treat and prevent tonic-clonic and psychomotor seizures. If phenytoin alone will not prevent seizure activity, coadministration with phenobarbital is usually effective. Initial therapy with phenytoin is started at doses of 100 to 300 mg/day for adults or 4 mg/kg/day for children. Because absorption is variable and the drug exhibits zero-order (nonlinear) kinetics, dose must be adjusted within 5 days using blood concentration to guide therapy. Oral bioavailability ranges from 80% to 95% and is diet-dependent. Phenytoin exhibits zero-order pharmacokinetics; the rate of clearance of the drug is dependent upon the concentration of drug present. Therefore, phenytoin does not have a classical half-life like other drugs, since it varies with blood concentration. At a blood concentration of 15 mcg/mL, approximately half the drug in the patient's body will be eliminated in 20 hours. As the blood concentration drops, the rate at which phenytoin is excreted increases. Phenytoin has a volume of distribution of 0.65 L/kg, and is highly protein bound (90%), mostly to albumin. Some drug side-effects occur in the therapeutic range; these include gingival hyperplasia, hyperglycemia, and skin rash. Phenytoin pharmacokinetics are significantly affected by a number of other drugs. As noted above, phenytoin and phenobarbital are frequently coadministered. Induction of the cytochrome P450 enzyme system by phenobarbital will increase the rate at which phenytoin is metabolized and cleared. At steady-state, enzyme induction will increase the rate of clearance of phenytoin such that the dose must be increased approximately 30% to maintain therapeutic levels. Uremia has a similar effect on phenytoin protein binding. In uremia, by-products of normal metabolism accumulate and bind to albumin, displacing phenytoin, which causes an increase in the free (active) fraction. Concurrent use of phenytoin and valproic acid (another frequently used antiepileptic) may result in altered valproic acid levels and/or altered phenytoin levels. Due to the complex situation involving displacement of protein-bound phenytoin and inhibition of phenytoin metabolism, as well as the potential
for decreased valproic acid concentrations, patients should be monitored for both phenytoin toxicity and therapeutic efficacy. Free phenytoin levels should be measured to provide the most accurate assessment of phenytoin activity early in therapy. At steady-state, free phenytoin and free valproic acid concentrations should be normalized. The free phenytoin level is the best indicator of adequate therapy in renal failure. In renal failure, the opportunity for the free phenytoin fraction to be cleared is significantly reduced. The end result is that both the total and free concentration of phenytoin increase, with the free concentration increasing faster than the total. Dosage must be reduced to avoid toxicity. Accordingly, the free phenytoin level is the best indicator of adequate therapy in renal failure. Toxicity is a constant possibility because of the manner in which phenytoin is metabolized. Small increases in dose can lead to very large increases in blood concentration, resulting in early signs of toxicity such as nystagmus, ataxia, and dysarthria. Severe toxicity occurs when the blood concentration is above 30 mcg/mL and is typified by tremor, hyperreflexia, and lethargy. The outcome of phenytoin toxicity is not as serious as phenobarbital because phenytoin is not a central nervous system sedative.

**Useful For:** Monitoring for appropriate therapeutic concentration Assessing compliance or toxicity

**Interpretation:** Dose should be adjusted to achieve steady-state total phenytoin concentrations between 10.0 and 20.0 mcg/mL. In patients with renal failure, total phenytoin is likely to be less than the therapeutic range of 10.0 to 20.0 mcg/mL. Severe toxicity occurs when the total blood concentration exceeds 30.0 mcg/mL.

**Reference Values:**
Therapeutic: 10.0-20.0 mcg/mL
Critical value: > or =30.0 mcg/mL

**Clinical References:**

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**Phoma betae, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L
Interpretation
0 Negative
1. 0.35-0.69   Equivocal
2. 0.70-3.49   Positive
3. 3.50-17.4   Positive
4. 17.5-49.9   Strongly positive
5. 50.0-99.9   Strongly positive
6. > or =100   Strongly positive Reference values apply to all ages.


FPGA
58042

Phosphatidylglycerol Antibodies, IgG, IgM and IgA

Reference Values:
Phosphatidylglycerol Antibody, IgG:
0  U/mL:  Normal
12  U/mL:  Equivocal. Suggest repeat testing in 4-6 weeks or consider antibody testing for cardiolipin IgG and IgM, beta-2 glycoprotein 1 IgG and IgM and lupus anticoagulant.
19  U/mL or greater:  Positive

Phosphatidylglycerol Antibody, IgM:
0  U/mL:  Normal
12  U/mL:  Equivocal. Suggest repeat testing in 4-6 weeks or consider antibody testing for cardiolipin IgG and IgM, beta-2 glycoprotein 1 IgG and IgM and lupus anticoagulant.
19  U/mL or greater:  Positive

Phosphatidylglycerol Antibody, IgA:
0  U/mL:  Normal
12  U/mL:  Equivocal. Suggest repeat testing in 4-6 weeks or consider antibody testing for cardiolipin IgG and IgM, beta-2 glycoprotein 1 IgG and IgM and lupus anticoagulant.
19  U/mL or greater:  Positive

FPHAB
57371

Phosphatidylinositol Antibodies, IgG, IgM and IgA

Reference Values:
Phosphatidylinositol Antibody IgG  (0 18) U/mL
Phosphatidylinositol Antibody IgM  (0 18) U/mL
Phosphatidylinositol Antibody IgA  (0 18) U/mL

0  U/mL:  Normal
12  U/mL:  Equivocal. Suggest repeat testing in 4-6 weeks or consider antibody testing for cardiolipin IgG and IgM, beta-2 glycoprotein 1 IgG and IgM and lupus anticoagulant.
19 or greater  U/mL:  Positive

PSPT
64704

Phosphatidylserine/Prothrombin Antibody, IgG and IgM, Serum

Clinical Information: A diagnosis of antiphospholipid syndrome (APS) is based on clinical and laboratory evaluation. The clinical manifestations associated with APS include arterial and venous thrombosis and recurrent pregnancy loss. The laboratory testing for APS focuses on assessment for autoantibodies specific for phospholipid/protein cofactor complexes. The current criteria require detection
of anticardiolipin, anti-beta 2-glycoprotein I, or lupus anticoagulant (LAC) for classification of APS. Cardiolipin is an anionic phospholipid that interacts with the protein cofactor beta 2-glycoprotein I. Anticardiolipin and anti-beta 2-glycoprotein I antibodies are detected by immunoassay using the antigen of cardiolipin/beta 2-glycoprotein I or purified beta 2-glycoprotein I, respectively. LAC is an indirect assessment for the presence of antiphospholipid antibodies, which is evident in the in vitro prolongation of phospholipid-dependent coagulation. There is evidence to suggest that patients with APS may develop autoantibodies to other phospholipid/protein complexes, specifically phosphatidylserine/prothrombin (PS/PT). Similar to cardiolipin/beta 2-glycoprotein I, PS/PT is a complex composed of the anionic phospholipid phosphatidylserine and the protein cofactor prothrombin. A recent systematic review has demonstrated that anti-PS/PT antibodies are a significant risk factor for arterial and venous thrombotic events, with an odds ratio of 5.11 (4.2-6.3). In addition, a separate study indicated that anti-PS/PT antibodies showed the highest correlation with LAC, compared to anticardiolipin or anti-beta 2-glycoprotein I antibodies (p=0.002). Anti-PS/PT antibodies may be a useful additional marker for evaluation of patients with suspected APS, particularly for those individuals with evidence of thrombosis or abnormal LAC testing.

**Useful For:** Evaluation of patients with suspected antiphospholipid syndrome Evaluation of patients with a strong suspicion of antiphospholipid syndrome for whom anticardiolipin/beta 2-glycoprotein I and anti-beta 2-glycoprotein I antibody testing was negative Evaluation of patients with evidence of a functional lupus anticoagulant Detection of both IgM and IgG antibodies against phosphatidylserine/prothrombin

**Interpretation:** A positive result is consistent with the presence of an antibody specific for the phosphatidylserine/prothrombin complex, and may be consistent with a diagnosis of antiphospholipid syndrome (APS) in patients with evidence of arterial or venous thrombosis or recurrent pregnancy loss. A negative result is consistent with the absence of an antibody specific for the phosphatidylserine/prothrombin complex. However, this does not exclude the diagnosis of APS, as other phospholipid/protein antibodies are also associated with this disorder.

**Reference Values:**
Negative < or =30.0 U
Borderline 30.1-40.0 U
Positive > or =40.1 U

**Clinical References:**

**Phosphatidylserine/Prothrombin Antibody, IgG, Serum**

**Clinical Information:** A diagnosis of antiphospholipid syndrome (APS) is based on clinical and laboratory evaluation. The clinical manifestations associated with APS include arterial and venous thrombosis and recurrent pregnancy loss. The laboratory testing for APS focuses on assessment for autoantibodies specific for phospholipid/protein cofactor complexes. The current criteria require detection of anticardiolipin, anti-beta 2-glycoprotein I, or lupus anticoagulant (LAC) for classification of APS. Cardiolipin is an anionic phospholipid that interacts with the protein cofactor beta 2-glycoprotein I. Anticardiolipin and anti-beta 2-glycoprotein I antibodies are detected by immunoassay using the antigen of cardiolipin/beta 2-glycoprotein I or purified beta 2-glycoprotein I, respectively. LAC is an indirect assessment for the presence of antiphospholipid antibodies, which is evident in the in vitro prolongation of phospholipid-dependent coagulation.
vitro prolongation of phospholipid-dependent coagulation. There is evidence to suggest that patients with APS may develop autoantibodies to other phospholipid/protein complexes, specifically phosphatidylserine/prothrombin (PS/PT). Similar to cardiolipin/beta 2-glycoprotein I, PS/PT is a complex composed of the anionic phospholipid phosphatidylserine and the protein cofactor prothrombin. A recent systematic review has demonstrated that anti-PS/PT antibodies are a significant risk factor for arterial and venous thrombotic events, with an odds ratio of 5.11 (4.2-6.3). In addition, a separate study indicated that anti-PS/PT antibodies showed the highest correlation with LAC, compared to anticardiolipin or anti-beta 2-glycoprotein I antibodies (p=0.002). Anti-PS/PT antibodies may be a useful additional marker for evaluation of patients with suspected APS, particularly for those individuals with evidence of thrombosis or abnormal LAC testing.

**Useful For:** Evaluation of patients with suspected antiphospholipid syndrome Evaluation of patients with a strong suspicion of antiphospholipid syndrome for whom anticardiolipin/beta 2-glycoprotein I and anti-beta 2-glycoprotein I antibody testing was negative Evaluation of patients with evidence of a functional lupus anticoagulant Detection of IgG antibodies against phosphatidylserine/prothrombin

**Interpretation:** A positive result is consistent with the presence of an antibody specific for the phosphatidylserine/prothrombin complex, and may be consistent with a diagnosis of antiphospholipid syndrome (APS) in patients with evidence of arterial or venous thrombosis or recurrent pregnancy loss. A negative result is consistent with the absence of an antibody specific for the phosphatidylserine/prothrombin complex. However, this does not exclude the diagnosis of APS, as other phospholipid/protein antibodies are also associated with this disorder.

**Reference Values:**
Negative ≤ or =30.0 U
Borderline 30.1-40.0 U
Positive > or =40.1 U

**Clinical References:**

**Phosphatidylserine/Prothrombin Antibody, IgM, Serum**

**Clinical Information:** A diagnosis of antiphospholipid syndrome (APS) is based on clinical and laboratory evaluation. The clinical manifestations associated with APS include arterial and venous thrombosis and recurrent pregnancy loss. The laboratory testing for APS focuses on assessment for autoantibodies specific for phospholipid/protein cofactor complexes. The current criteria require detection of anticardiolipin, anti-beta 2-glycoprotein I, or lupus anticoagulant (LAC) for classification of APS. Cardiolipin is an anionic phospholipid that interacts with the protein cofactor beta 2-glycoprotein I. Anticardiolipin and anti-beta 2-glycoprotein I antibodies are detected by immunoassay using the antigen of cardiolipin/beta 2-glycoprotein I or purified beta 2-glycoprotein I, respectively. LAC is an indirect assessment for the presence of antiphospholipid antibodies, which is evident in the in vitro prolongation of phospholipid-dependent coagulation. There is evidence to suggest that patients with APS may develop autoantibodies to other phospholipid/protein complexes, specifically phosphatidylserine/prothrombin (PS/PT). Similar to cardiolipin/beta 2-glycoprotein I, PS/PT is a complex composed of the anionic phospholipid phosphatidylserine and the protein cofactor prothrombin. A recent systematic review has demonstrated that anti-PS/PT antibodies are a significant risk factor for arterial and venous thrombotic events, with an odds ratio of 5.11 (4.2-6.3). In addition, a separate study indicated that anti-PS/PT
antibodies showed the highest correlation with LAC, compared to anticardiolipin or anti-beta 2-glycoprotein I antibodies (p=0.002). Anti-PS/PT antibodies may be a useful additional marker for evaluation of patients with suspected APS, particularly for those individuals with evidence of thrombosis or abnormal LAC testing.

**Useful For:** Evaluation of patients with suspected antiphospholipid syndrome Evaluation of patients with a strong suspicion of antiphospholipid syndrome for whom anticardiolipin/beta 2-glycoprotein I and anti-beta 2-glycoprotein I antibody testing was negative Evaluation of patients with evidence of a functional lupus anticoagulant Detection of IgM antibodies against phosphatidylycerine/prothrombin

**Interpretation:** A positive result is consistent with the presence of an antibody specific for the phosphatidylycerine/prothrombin complex, and may be consistent with a diagnosis of antiphospholipid syndrome (APS) in patients with evidence of arterial or venous thrombosis or recurrent pregnancy loss. A negative result is consistent with the absence of an antibody specific for the phosphatidylycerine/prothrombin complex. However, this does not exclude the diagnosis of APS, as other phospholipid/protein antibodies are also associated with this disorder.

**Reference Values:**
- Negative < or =30.0 U
- Borderline 30.1-40.0 U
- Positive > or =40.1 U

**Clinical References:**

**PLAIF 70592**

**Phospholipase A2 Receptor (PLA2R) Frozen IF, Renal**

**Clinical Information:** Membranous nephropathy is the most common cause of nephrotic syndrome in white adults. Eighty-five percent of membranous nephropathy cases are primary or idiopathic and the other 15% are secondary. Phospholipase A2 receptor (PLA2R) is an antigen located on podocytes. The majority of cases of primary membranous nephropathy have circulating autoantibodies against PLA2R.

**Useful For:** Distinguishing primary membranous nephropathy from secondary membranous nephropathy

**Interpretation:** This test, (when not accompanied by a pathology consultation request) will be reported as either positive or negative. If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test and send the corresponding renal pathology light microscopy and immunofluorescence (IF) slides (or IF images on a CD), electron microscopy images (prints or CD), and the pathology report.

**Clinical References:**
4. Larsen CP, Walker PD: Phospholipase A2 receptor (PLA2R) staining is useful in the determination of de novo versus recurrent membranous glomerulopathy. Transplantation
Phospholipase A2 Receptor Antibodies, Serum

**Clinical Information:** Membranous nephropathy (MN) is a rare disease in which immune complexes deposit at the glomerular basement membrane, causing damage to the filtration barrier, resulting in proteinuria. Recent studies have shown that in approximately 70% of patients with primary MN (pMN), the immune complexes consist of autoantibodies against the podocyte protein M-type phospholipase A2 receptor (PLA2R).(1) There is also evidence that levels of anti-PLA2R autoantibodies correlate well with disease activity and progression.(2) The presence of anti-PLA2R antibodies could also potentially be used to differentiate pMN from other causes of nephrotic syndrome if a biopsy is not possible. Among patients with chronic kidney disease (CKD) awaiting kidney transplantation, higher levels of anti-PLA2R could predict those more likely to recur after transplantation.(2)

**Useful For:** Distinguishing primary from secondary membranous nephropathy

**Interpretation:** Therapy outcome can be monitored by measuring the anti-phospholipase A2 receptor (PLA2R) antibody titer. A titer increase, decrease, or disappearance generally precedes a change in clinical status. Thus, the determination of the antibody titer has a high predictive value with respect to clinical remission, relapse, or risk assessment after kidney transplantation.

**Reference Values:**

**ELISA:**
- Negative: <14 RU/mL
- Borderline: > or =14-<20 RU/mL
- Positive: > or =20 RU/mL

**IFA:** Negative


Phospholipase A2 Receptor, Enzyme Linked Immunosorbent Assay, Serum

**Reference Values:**
For more information see PLA2R / Phospholipase A2 Receptor Antibodies, Serum.

Phospholipase A2 Receptor, Indirect Immunofluorescence Assay, Serum

**Reference Values:**
For more information see PLA2R / Phospholipase A2 Receptor Antibodies, Serum.

Phospholipid (Cardiolipin) Antibodies, IgA, Serum

**Clinical Information:** The plasma membranes of mammalian cells are formed from phospholipids. Anionic phospholipids (eg, phosphatidylserine) are found on the cytoplasmic surface and neutral phospholipids (eg, phosphatidylcholine) predominate on the external surface. Membrane phospholipids participate in several important cellular functions including exchanging metabolites across membranes,
transferring molecular signals and serving as a platform for the assembly of protein-lipid complexes. Cellular activation is often accompanied by the translocation of anionic phospholipids to the external membrane surface. For example, during platelet-mediated blood coagulation, phosphatidylserine is translocated from the inner platelet membrane and provides a surface for the assembly of the prothrombinase enzyme complex that catalyzes the formation of thrombin. Complexes of negatively charged (anionic) phospholipids and endogenous plasma proteins provide epitopes recognized by natural autoantibodies. Plasma from normal individuals contains low concentrations of natural IgG autoantibodies of moderate affinity. Pathologic levels of autoantibodies reflect loss of tolerance and increased production of antibodies. These autoantibodies are called phospholipid or cardiolipin antibodies when they are detected by immunoassays that employ anionic phospholipids as substrates. The most commonly used phospholipid substrate is cardiolipin. The term phospholipid antibody is actually a misnomer. The autoantibodies react with epitopes of protein molecules that associate noncovalently with reagent phospholipids. The best characterized phospholipid-binding protein is beta 2-glycoprotein 1 (beta-2 GP1) and most immunoassays for phospholipid antibodies employ a composite substrate consisting of cardiolipin plus beta-2 GP1. Beta-2 GP1 is a 326-amino acid polypeptide that contains 5 homologous domains of approximately 60 amino acids each. Most phospholipid antibodies bind to an epitope associated with domain 1 near the N-terminus. Autoantibodies can also be detected by the use of functional, phospholipid-dependent coagulation assays. Phospholipid antibodies detected by functional assays are often called lupus anticoagulants because they produce prolongation of phospholipid-dependent clotting in vitro and are found in some patients with systemic lupus erythematosus. Not all phospholipid antibodies possess lupus anticoagulant activity. Only those phospholipid antibodies that are capable of cross-linking beta-2 GP1 molecules can interact efficiently with phospholipid surfaces in functional coagulation assays. It is hypothesized that complexes formed in vivo between bivalent, natural autoantibodies and beta-2 GP1 bind to translocated, anionic phospholipid on activated platelets at sites of endothelial injury. This binding is believed to promote further platelet activation that may lead to thrombosis. Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by thromboses, complications of pregnancy, and certain laboratory abnormalities. The diagnosis of APS requires at least 1 clinical criteria and 1 laboratory criteria be met. The clinical criteria include vascular thrombosis (arterial or venous in any organ or tissue) and pregnancy morbidity (unexplained fetal death, premature birth, severe preeclampsia, or placental insufficiency). Other clinical manifestations, including heart valve disease, livedo reticularis, thrombocytopenia, nephropathy and neurological symptoms, are often associated with APS but are not included in the diagnostic criteria. The laboratory criteria for diagnosis of APS are presence of lupus anticoagulant, presence of IgG and/or IgM anticardiolipin antibody (>40 GPL, >40 MPL, or >99th percentile), and/or presence of IgG and/or IgM anti-beta-2 GP1 antibody (99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks. Anticardiolipin and anti-beta-2 GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity. Evaluation of patients with suspected antiphospholipid syndrome by identification of phospholipid IgA antibodies

**Useful For:** Evaluation of patients with suspected antiphospholipid syndrome by identification of phospholipid IgA antibodies

**Interpretation:** APL, GPL and MPL units refer to arbitrary units. The abbreviation APL denotes the result is from the IgA isotype, the abbreviation GPL denotes the result is from the IgG isotype and the abbreviation MPL denotes the result is from the IgM isotype. The letters "PL" denote specificity for phospholipid antigens. Positive and strongly-positive results for IgG and IgM phospholipid (cardiolipin) antibodies (>40 GPL and/or >40 MPL) are diagnostic criteria for antiphospholipid syndrome (APS). Lesser levels of IgG and IgM phospholipid (cardiolipin) antibodies and antibodies of the IgA isotype (APL) may occur in patients with clinical signs of APS but the results are not considered diagnostic. Phospholipid (cardiolipin) antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. IgA phospholipid (cardiolipin) antibody results >15 APL with negative IgG and IgM phospholipid (cardiolipin) antibody results are not diagnostic for APS. Detection of phospholipid (cardiolipin) antibodies is not affected by anticoagulant treatment.

**Reference Values:**

- <15.0 APL (negative)
- 15.0-39.9 APL (weakly positive)
- 40.0-79.9 APL (positive)
- > or =80.0 APL (strongly positive)

APL refers to IgA Phospholipid Units. One APL unit is 1 microgram of IgA antibody.

Phospholipid (Cardiolipin) Antibodies, IgG and IgM, Serum

Clinical Information: The plasma membranes of mammalian cells are formed from phospholipids. Anionic phospholipids (e.g., phosphatidylserine) are found on the cytoplasmic surface and neutral phospholipids (e.g., phosphatidylcholine) predominate on the external surface. Membrane phospholipids participate in several important cellular functions including exchanging metabolites across membranes, transferring molecular signals and serving as a platform for the assembly of protein-lipid complexes. Cellular activation is often accompanied by the translocation of anionic phospholipids to the external membrane surface. For example, during platelet-mediated blood coagulation phosphatidylserine is translocated from the inner platelet membrane and provides a surface for the assembly of the prothrombinase enzyme complex that catalyzes the formation of thrombin. Complexes of negatively charged (anionic) phospholipids and endogenous plasma proteins provide epitopes recognized by natural autoantibodies. Plasma from normal individuals contains low concentrations of natural IgG autoantibodies of moderate affinity. Pathologic levels of autoantibodies reflect loss of tolerance and increased production of antibodies. These autoantibodies are called phospholipid or cardiolipin antibodies when they are detected by immunoassays that employ anionic phospholipids as substrates. The most commonly used phospholipid substrate is cardiolipin. The term phospholipid antibody is actually a misnomer. The autoantibodies react with epitopes of protein molecules that associate noncovalently with reagent phospholipids. The best characterized phospholipid-binding protein is beta 2 glycoprotein 1 and most immunoassays for phospholipid antibodies employ a composite substrate consisting of cardiolipin plus beta-2 glycoprotein 1(beta-2 GP1). Beta-2 GP1 is a 326 amino acid polypeptide that contains 5 homologous domains of approximately 60 amino acids each. Most phospholipid antibodies bind to an epitope associated with domain 1 near the N-terminus. Autoantibodies can also be detected by the use of functional, phospholipid-dependent coagulation assays. Phospholipid antibodies detected by functional assays are often called lupus anticoagulants because they produce prolongation of phospholipid-dependent clotting in vitro. Not all phospholipid antibodies possess lupus anticoagulant activity. Only those phospholipid antibodies that are capable of cross-linking beta-2 GP1 molecules can interact efficiently with phospholipid surfaces in functional coagulation assays. It is hypothesized that complexes formed in vivo between bivalent, natural autoantibodies and beta-2 GP1 bind to translocated, anionic phospholipid on activated platelets at sites of endothelial injury. This binding is believed to promote further platelet activation that may lead to thrombosis. Phospholipid antibodies occur in patients with a variety of clinical signs and symptoms notably thrombosis (arterial or venous) pregnancy morbidity (unexplained fetal death, premature birth, severe preeclampsia, or placental insufficiency) unexplained cutaneous circulation disturbances (livido reticularis or pyoderma gangrenosum) thrombocytopenia or hemolytic anemia and nonbacterial thrombotic endocarditis. Phospholipid antibodies and lupus anticoagulants are found with increased frequency in patients with systemic rheumatic diseases especially lupus erythematosus. The term antiphospholipid syndrome (APS) or Hughes syndrome is used to describe the triad of thrombosis, recurrent fetal loss and thrombocytopenia accompanied by phospholipid antibodies or a lupus anticoagulant. The diagnosis of APS requires 1 or more of the above mentioned clinical findings plus positive test results for phospholipid antibodies (> or =40 GPL or MPL) or positive tests for a lupus anticoagulant on more than 1 occasion separated by at least 6 weeks.

Useful For: Testing for phospholipid antibodies is indicated in the following clinical situations:
- Unexplained arterial or venous thrombosis - A history of pregnancy morbidity defined as 1 or more unexplained deaths of a morphologically normal fetus beyond the 10th week of gestation, 1 or more premature births before 34 weeks of gestation caused by severe preeclampsia or placental insufficiency, or 3 or more unexplained, consecutive spontaneous abortions before the 10th week of gestation with no identifiable maternal hormonal or anatomic, or maternal or paternal chromosomal causes - Presence of an unexplained cutaneous circulatory disturbance, eg, livedo reticularis or pyoderma gangrenosum - Presence of a systemic rheumatic disease especially lupus erythematosus - Unexplained thrombocytopenia or hemolytic anemia - Possible nonbacterial, thrombotic endocarditis

**Interpretation:** Positive and strongly positive results for phospholipid antibodies (> or =40 GPL and/or MPL) are a diagnostic criterion for antiphospholipid syndrome (APS). Lesser levels of phospholipid antibodies and antibodies of the IgA isotype may occur in patients with clinical signs of APS but the results are not considered diagnostic. Detection of phospholipid antibodies is not affected by anticoagulant treatment.

**Reference Values:**

- <15.0 MPL or GPL (negative)
- 15.0-39.9 MPL or GPL (weakly positive)
- 40.0-79.9 MPL or GPL (positive)
- > or =80.0 MPL or GPL (strongly positive)

MPL refers to IgM Phospholipid Units. One MPL unit is 1 microgram of IgM antibody.

GPL refers to IgG Phospholipid Units. One GPL unit is 1 microgram of IgG antibody.

Reference values apply to all ages.

**Clinical References:**


**Phospholipid (Cardiolipin) Antibodies, IgG, Serum**

**Clinical Information:** The plasma membranes of mammalian cells are formed from phospholipids. Anionic phospholipids (e.g., phosphatidylserine) are found on the cytoplasmic surface and neutral phospholipids (e.g., phosphatidylcholine) predominate on the external surface. Membrane phospholipids participate in several important cellular functions including exchanging metabolites across membranes, transferring molecular signals and serving as a platform for the assembly of protein-lipid complexes. Cellular activation is often accompanied by the translocation of anionic phospholipids to the external membrane surface. For example, during platelet-mediated blood coagulation phosphatidylserine is translocated from the outer platelet membrane and provides a surface for the assembly of the prothrombinase enzyme complex that catalyzes the formation of thrombin. Complexes of negatively charged (anionic) phospholipids and endogenous plasma proteins provide epitopes recognized by natural autoantibodies. Plasma from normal individuals contains low concentrations of natural IgG autoantibodies of moderate affinity. Pathologic levels of autoantibodies reflect loss of tolerance and increased production of antibodies. These autoantibodies are called phospholipid or cardiolipin antibodies when they are detected by immunoassays that employ anionic phospholipids as substrates. The most commonly used phospholipid substrate is cardiolipin. The term phospholipid antibody is actually a misnomer. The autoantibodies react with epitopes of protein molecules that associate noncovalently with reagent phospholipids. The best characterized phospholipid-binding protein is beta-2 glycoprotein 1 (beta-2 GP1) and most immunoassays for phospholipid antibodies employ this as their phospholipid substrate.

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composite substrate consisting of cardiolipin plus beta-2 GP1. Beta-2 GP1 is a 326-amino acid polypeptide that contains 5 homologous domains of approximately 60 amino acids each. Most phospholipid antibodies bind to an epitope associated with domain 1 near the N-terminus. Autoantibodies can also be detected by the use of functional, phospholipid-dependent coagulation assays. Phospholipid antibodies detected by functional assays are often called lupus anticoagulants because they produce prolongation of phospholipid-dependent clotting in vitro and are found in some patients with systemic lupus erythematosus. Not all phospholipid antibodies possess lupus anticoagulant activity. (3) Only those phospholipid antibodies that are capable of cross-linking beta-2 GP1 molecules can interact efficiently with phospholipid surfaces in functional coagulation assays. It is hypothesized that complexes formed in vivo between bivalent, natural autoantibodies and beta-2 GP1 bind to translocated, anionic phospholipid on activated platelets at sites of endothelial injury. This binding is believed to promote further platelet activation that may lead to thrombosis. Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by thromboses, complications of pregnancy, and certain laboratory abnormalities. The diagnosis of APS requires at least 1 clinical criteria and 1 laboratory criteria be met. (4) The clinical criteria include vascular thrombosis (arterial or venous in any organ or tissue) and pregnancy morbidity (unexplained fetal death, prematurity, birth, severe preeclampsia, or placental insufficiency). Other clinical manifestations, including heart valve disease, livedo reticularis, thrombocytopenia, nephropathy and neurological symptoms, are often associated with APS but are not included in the diagnostic criteria. The laboratory criteria for diagnosis of APS are the presence of lupus anticoagulant, the presence of IgG and/or IgM anticardiolipin antibody (>40 GPL, >40 MPL, or >99th percentile), and/or the presence of IgG and/or IgM anti-beta-2 GP1 antibody (>99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks. Anticardiolipin and beta GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity. (4)

**Useful For:** Evaluation of patients with suspected antiphospholipid syndrome by identification of phospholipid IgG antibodies

**Interpretation:** APL, GPL, and MPL units refer to arbitrary units. The abbreviation APL denotes the result is from the IgA isotype, the abbreviation GPL denotes the result is from the IgG isotype and the abbreviation MPL denotes the result is from the IgM isotype. The letters "PL" denote specificity for phospholipid antigens. Positive and strongly-positive results for IgG and IgM phospholipid (cardiolipin) antibodies (>40 GPL and/or >40 MPL) are diagnostic criteria for antiphospholipid syndrome (APS). Lesser levels of IgG and IgM phospholipid (cardiolipin) antibodies and antibodies of the IgA isotype may occur in patients with clinical signs of APS but the results are not considered diagnostic. Phospholipid (cardiolipin) antibodies must be detected on 2 or more occasions at least 12 weeks apart to fulfill the laboratory diagnostic criteria for APS. An IgA phospholipids (cardiolipin) antibody result above 15 APL with negative IgG and IgM phospholipids (cardiolipin) antibody results is not diagnostic for APS. Detection of phospholipid (cardiolipin) antibodies is not affected by anticoagulant treatment.

**Reference Values:**

- <15.0 GPL (negative)
- 15.0-39.9 GPL (weakly positive)
- 40.0-79.9 GPL (positive)
- > or =80.0 GPL (strongly positive)

GPL refers to IgG Phospholipid Units. One GPL unit is 1 microgram of IgG antibody.

Reference values apply to all ages.

**Clinical References:**

Clinical Information: The plasma membranes of mammalian cells are formed from phospholipids. Anionic phospholipids (e.g., phosphatidylserine) are found on the cytoplasmic surface and neutral phospholipids (e.g., phosphatidylcholine) predominate on the external surface. Membrane phospholipids participate in several important cellular functions including exchanging metabolites across membranes, transferring molecular signals and serving as a platform for the assembly of protein-lipid complexes. Cellular activation is often accompanied by the translocation of anionic phospholipids to the external membrane surface. For example, during platelet-mediated blood coagulation, phosphatidylserine is translocated from the inner platelet membrane and provides a surface for the assembly of the prothrombinase enzyme complex that catalyzes the formation of thrombin. Complexes of negatively charged (anionic) phospholipids and endogenous plasma proteins provide epitopes recognized by natural autoantibodies. Plasma from normal individuals contains low concentrations of natural IgG autoantibodies of moderate affinity. Pathologic levels of autoantibodies reflect loss of tolerance and increased production of antibodies. These autoantibodies are called phospholipid or cardiolipin antibodies when they are detected by immunoassays that employ anionic phospholipids as substrates. The most commonly used phospholipid substrate is cardiolipin. The term phospholipid antibody is actually a misnomer. The autoantibodies react with epitopes of protein molecules that associate noncovalently with reagent phospholipids. The best characterized phospholipid-binding protein is beta-2 glycoprotein 1 (beta-2 GP1) and most immunoassays for phospholipid antibodies employ a composite substrate consisting of cardiolipin plus beta-2 GP1. Beta-2 GP1 is a 326-amino acid polypeptide that contains 5 homologous domains of approximately 60 amino acids each. Most phospholipid antibodies bind to an epitope associated with domain 1 near the N-terminus. Autoantibodies can also be detected by the use of functional, phospholipid-dependent coagulation assays. Phospholipid antibodies detected by functional assays are often called lupus anticoagulants because they produce prolongation of phospholipid-dependent clotting in vitro and are found in some patients with systemic lupus erythematosus. Not all phospholipid antibodies possess lupus anticoagulant activity. Only those phospholipid antibodies that are capable of cross-linking beta-2 GP1 molecules can interact efficiently with phospholipid surfaces in functional coagulation assays. It is hypothesized that complexes formed in vivo between bivalent, natural autoantibodies and beta-2 GP1 bind to translocated, anionic phospholipid on activated platelets at sites of endothelial injury. This binding is believed to promote further platelet activation that may lead to thrombosis. Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by thromboses, complications of pregnancy, and certain laboratory abnormalities. The diagnosis of APS requires at least 1 clinical criteria and 1 laboratory criteria be met. The clinical criteria include vascular thrombosis (arterial or venous in any organ or tissue) and pregnancy morbidity (unexplained fetal death, premature birth, severe preeclampsia, or placental insufficiency). Other clinical manifestations, including heart valve disease, livedo reticularis, thrombocytopenia, nephropathy and neurological symptoms, are often associated with APS but are not included in the diagnostic criteria. The laboratory criteria for diagnosis of APS are the presence of lupus anticoagulant, the presence of IgG and/or IgM anticardiolipin antibody (>40 GPL, >40 MPL, or >99th percentile), and/or the presence of IgG and/or IgM anti-beta-2 GP 1 antibody (>99th percentile). All antibodies must be demonstrated on 2 or more occasions separated by at least 12 weeks. Anticardiolipin and anti-beta-2 GP1 antibodies of the IgA isotype are not part of the laboratory criteria for APS due to lack of specificity. Use of patients with suspected antiphospholipid syndrome by identification of phospholipid IgM antibodies

Useful For: Evaluation of patients with suspected antiphospholipid syndrome by identification of phospholipid IgM antibodies

Interpretation: APL, GPL, and MPL units refer to arbitrary units. The abbreviation APL denotes the result is from the IgA isotype, the abbreviation GPL denotes the result is from the IgG isotype and the abbreviation MPL denotes the result is from the IgM isotype. The letters "PL" denote specificity for phospholipid antigens. Positive and strongly-positive results for IgG and IgM phospholipid (cardiolipin) antibodies (>40 GPL and/or >40 MPL) are diagnostic criteria for antiphospholipid syndrome (APS). Lesser levels of IgG and IgM phospholipid (cardiolipin) antibodies and antibodies of the IgA isotype may occur in patients with clinical signs of APS but the results are not considered diagnostic. Phospholipid (cardiolipin) antibodies must be detected on 2 or more occasions at least 12 weeks apart to
fulfill the laboratory diagnostic criteria for APS. An IgA phospholipid (cardiolipin) antibody result above 15 MPL with negative IgG and IgM phospholipids (cardiolipin) antibody results is not diagnostic for APS. Detection of phospholipid (cardiolipin) antibodies is not affected by anticoagulant treatment.

Reference Values:
<15.0 MPL (negative)
15.0-39.9 MPL (weakly positive)
40.0-79.9 MPL (positive)
> or =80.0 MPL (strongly positive)

MPL refers to IgM Phospholipid Units. One MPL unit is 1 microgram of IgM antibody. Reference values apply to all ages.


Phospholipids, Serum

Clinical Information: The phospholipids comprise about 1/3 of the total lipids in serum. These consist in a large part of a lipid, phosphatidylcholine (formerly lecithin), in which 1 of the glycerol carbons is esterified with choline phosphate. A major step in lipoprotein particle remodeling results from lecithin-cholesterol acyltransferase (LCAT) activity, which normally transesterifies free cholesterol with fatty acids derived from phosphatidylcholine. LCAT deficiency results in a lack of remodeling of primary lipoprotein particles, affecting eventual cholesterol uptake and elimination. In cases of deficiency of LCAT, the concentration of lecithin in the serum are increased several-fold. Clinical findings in LCAT deficiency include corneal opacities, anemia, and frequently, proteinuria. The disorder is inherited as an autosomal recessive trait. Early atherosclerosis develops in many individuals with this disorder. In addition, sphingomyelin normally comprises about 5% to 20% of the total phospholipids of serum. In Niemann-Pick Type A and B diseases, sphingomyelin accumulates in visceral and neural tissues and may become increased in the serum. Other disorders involving alterations of the concentration, composition, and/or lipoprotein distribution include: abeta- or hypobetalipoproteinemia, Tangier disease, or fish eye disease.

Useful For: First-order test in the diagnosis of lecithin-cholesterol acyltransferase deficiency

Interpretation: Elevated in cases of lecithin-cholesterol acyltransferase deficiency deficiency due to elevations of lecithin

Reference Values:
155-275 mg/dL
Reference values have not been established for patients who are <16 years of age.

Phosphomannomutase (PMM) and Phosphomannose Isomerase (PMI), Leukocytes

Clinical Information: Congenital disorders of glycosylation (CDG), formerly known as carbohydrate-deficient glycoprotein syndrome, are a group of inherited metabolic diseases that affect one of the steps of the pathway involved in glycosylation. CDG typically present as multisystemic disorders and may include developmental delay, hypotonia, abnormal magnetic resonance imaging (MRI) findings, hypoglycemia, and protein-losing enteropathy. There is considerable variation in the severity of this group of diseases, which can range from hydrops fetalis to a mild presentation in adults. In some subtypes (Ib, in particular) intelligence is not compromised. Phosphomannomutase-2 deficiency (PMM2-CDG or CDG-Ia) is an autosomal recessive glycosylation disorder resulting from reduced or absent activity of the enzyme phosphomannomutase-2, encoded by the PMM2 gene. It is the most common CDG worldwide. Patients with CDG-Ia have moderate to severe neurological disease, more or less typical dysmorphology, and variable involvement of other organ systems. Severely affected individuals with CDG-Ia usually present in the neonatal period with failure to thrive, developmental delay, abnormal subcutaneous fat distribution, elevated liver transaminases, and abnormal MRI findings. Later presenting individuals can have clinical features that include ataxia, significantly delayed motor and language development, seizures, stroke-like episodes, retinitis pigmentosa, joint contractures and skeletal deformities. An adult stable disability type has also been described. Currently, there is no cure and treatment remains primarily supportive and symptomatic. Phosphomannose isomerase deficiency (MPI-CDG or CDG-Ib) is an autosomal recessive glycosylation disorder resulting from reduced or absent activity of phosphomannose isomerase, an enzyme encoded by the MPI gene. This CDG subtype is unique in that there is little to no involvement of the central nervous system. It is mainly hepatic-intestinal without dysmorphology, and the primary clinical manifestations are a result of aberrant gastrointestinal function. In particular, individuals with CDG-Ib may present with failure to thrive, hypoglycemia, chronic diarrhea, and protein-losing enteropathy. CDG-Ib is also unique in that it can be effectively treated with mannose supplementation, though it can be fatal if left untreated.

Useful For: Diagnosing congenital disorders of glycosylation Ia (phosphomannomutase-2 deficiency: CDG-Ia or PMM2-CDG) and Ib (phosphomannose isomerase deficiency: CDG-Ib or MPI-CDG) as measured in leukocytes Follow-up testing for patients with an abnormal transferrin isoform profile as determined by liquid chromatography-mass spectrometry (CDG / Carbohydrate Deficient Transferrin for Congenital Disorders of Glycosylation, Serum)

Interpretation: Normal results are not consistent with either phosphomannomutase-2 deficiency (PMM2-CDG or CDG-Ia) or phosphomannose isomerase deficiency (MPI-CDG or CDG-Ib). Markedly reduced activity of phosphomannomutase is consistent with a diagnosis of CDG-Ia. Markedly reduced activity of phosphomannose isomerase is consistent with a diagnosis of CDG-Ib. Mild to moderately reduced enzyme activities will be interpreted in the context of clinical and other laboratory test information submitted with the specimen.

Reference Values:
PHOSPHOMANNOMUTASE
Normal >350 nmol/h/mg protein

PHOSPHOMANNOSE ISOMERASE
Normal >1,300 nmol/h/mg protein

### Phosphorus (Inorganic), Serum

**Clinical Information:** Of the phosphorus contained in the body, 88% is localized in bone in the form of hydroxyapatite. The remainder is involved in intermediary carbohydrate metabolism and in physiologically important substances such as phospholipids, nucleic acids, and adenosine triphosphate (ATP). Phosphorus occurs in blood in the form of inorganic phosphate and organically bound phosphoric acid. The small amount of extracellular organic phosphorus is found exclusively in the form of phospholipids. Serum contains approximately 2.5 to 4.5 mg/dL of inorganic phosphate (the fraction measure in routine biochemical assays). Serum phosphate concentrations are dependent on meals and variation in the secretion of hormones such as parathyroid hormone (PTH) and may vary widely. Hypophosphatemia may have 4 general causes: shift of phosphate from extracellular to intracellular, renal phosphate wasting, loss from the gastrointestinal tract, and loss from intracellular stores. Hyperphosphatemia is usually secondary to an inability of the kidneys to excrete phosphate. Other factors may relate to increased intake or a shift of phosphate from the tissues into the extracellular fluid.

**Useful For:** Diagnosis and management of a variety of disorders including bone, parathyroid, and renal disease

**Interpretation:** Hypophosphatemia is relatively common in hospitalized patients. Serum concentrations of phosphate between 1.5 and 2.4 mg/dL may be considered moderately decreased and are not usually associated with clinical signs and symptoms. Levels below 1.5 mg/dL may result in muscle weakness, hemolysis of red cells, coma, and bone deformity and impaired growth. The most acute problem associated with rapid elevations of serum phosphate levels is hypocalemia with tetany, seizures, and hypotension. Soft tissue calcification is also an important long-term effect of high phosphorus levels. Phosphorus levels below 1.0 mg/dL are potentially life-threatening and are considered a critical value in the Mayo Health System.

**Reference Values:**

**Males**
- 1-4 years: 4.3-5.4 mg/dL
- 5-13 years: 3.7-5.4 mg/dL
- 14-15 years: 3.5-5.3 mg/dL
- 16-17 years: 3.1-4.7 mg/dL
- ≥ 18 years: 2.5-4.5 mg/dL

Reference values have not been established for patients that are less than 12 months of age.

**Females**
- 1-7 years: 4.3-5.4 mg/dL
- 8-13 years: 4.0-5.2 mg/dL
- 14-15 years: 3.5-4.9 mg/dL
- 16-17 years: 3.1-4.7 mg/dL
- ≥ 18 years: 2.5-4.5 mg/dL

Reference values have not been established for patients that are less than 12 months of age.


### Phosphorus, 24 Hour, Urine

**Clinical Information:** Approximately 80% of filtered phosphorus is reabsorbed by renal proximal tubule cells. The regulation of urinary phosphorus excretion is principally dependent on regulation of proximal tubule phosphorus reabsorption. A variety of factors influence renal tubular phosphate reabsorption, and consequent urine excretion. Factors which increase urinary phosphorus excretion include high phosphorus diet, parathyroid hormone, extracellular volume expansion, low dietary...
potassium intake and proximal tubule defects (eg, Fanconi Syndrome, X-linked hypophosphatemic Rickets, tumor-induced osteomalacia). Factors which decrease, or are associated with decreases in, urinary phosphorus excretion include low dietary phosphorus intake, insulin, high dietary potassium intake, and decreased intestinal absorption of phosphorus (eg, phosphate-binding antacids, vitamin D deficiency, malabsorption states). A renal leak of phosphate has also been implicated as contributing to kidney stone formation in some patients.

Useful For: Evaluation of hypo- or hyper-phosphatemic states Evaluation of patients with nephrolithiasis

Interpretation: Interpretation of urinary phosphorus excretion is dependent upon the clinical situation, and should be interpreted in conjunction with the serum phosphorus concentration.

Reference Values: <1,100 mg/24 hours


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**PHBF**

**Phosphorus, Body Fluid**

Clinical Information: Not available

Useful For: Not established

Interpretation: None available

Reference Values: Not applicable


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**RPOU**

**Phosphorus, Pediatric, Random, Urine**

Clinical Information: Approximately 80% of filter phosphorus is reabsorbed by renal proximal tubule cells. The regulation of urinary phosphorus excretion is principally dependent on regulation of proximal tubule phosphorus reabsorption. A variety of factors influence renal tubular phosphate reabsorption, and consequent urine excretion. Factors that increase urinary phosphorus excretion include high phosphorus diet, parathyroid hormone, extracellular volume expansion, low dietary potassium intake and proximal tubule defects (eg, Fanconi syndrome, X-linked hypophosphatemic rickets, tumor-induced osteomalacia). Factors that decrease, or are associated with decreases in, urinary phosphorus excretion include low dietary phosphorus intake, insulin, high dietary potassium intake, and decreased intestinal absorption of phosphorus (eg, phosphate-binding antacids, vitamin D deficiency, malabsorption states). A renal leak of phosphate has also been implicated as contributing to kidney stone formation in some patients. A timed 24-hour urine collection is the preferred specimen for measuring and interpreting this urinary analyte. Random collections normalized to urinary creatinine may be of some clinical use in patients who cannot collect a 24-hour specimen, typically small children. Therefore, this random test is offered for children <16 years old.

Useful For: Evaluation of hypo- or hyperphosphatemic states Evaluation of patients with nephrolithiasis

Interpretation: Interpretation of urinary phosphorus excretion is dependent upon the clinical situation, and should be interpreted in conjunction with the serum phosphorus concentration. Pediatric Reference Ranges on a Random Specimen Phosphate/Creatinine (mg/mg)(1) Age (year) 5th Percentile 95th Percentile 0-1 >0.34 <5.24 1-2 >0.34 <3.95 2-3 >0.34 <3.13 3-5 >0.33 <2.17 5-7 >0.33 <1.19 7-10 >0.32 <0.97 10-14 >0.22 <0.86 14-17 >0.21 <0.75

isd
Reference Values:
No established reference values

Clinical References:

Phosphorylated TDP43 Immunostain, Technical Component Only

Clinical Information: TAR DNA-binding protein 43 (TDP-43) has multiple functions in transcriptional repression, translational regulation, and pre-mRNA splicing. In normal cells, TDP-43 is found in the nucleus, whereas in affected cells TDP-43 is phosphorylated and found in intracytoplasmic inclusions and neurites. The phosphoTDP-43-specific antibody will only stain the intracytoplasmic inclusions and neurites, thus highlighting the patterns that are hallmarks for amyotrophic lateral sclerosis (ALS) and frontotemporal lobular degeneration.

Useful For: Identification of pathological forms of TDP-43 in neurodegenerative diseases

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

Phthalic Anhydride, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<td>2</td>
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<td>Positive</td>
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<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
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</tr>
<tr>
<td>6</td>
<td>&gt;or =100</td>
<td>Strongly positive</td>
</tr>
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</table>

Reference values apply to all ages.

clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


**PIGF**

**82145**

Pigeon Feathers, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


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**PIN2 (p63/p504S) Immunostain, Technical Component Only**

**Clinical Information:** Prostatic intraepithelial neoplasia (PIN) cocktail-2 is a cocktail including 2 antibodies directed against p63 (nuclear) and P504S (cytoplasm) used in the diagnosis of high-grade PIN and prostate cancer. p63 stains the nuclei of normal myoepithelial cells that surround the prostatic epithelial cells. This myoepithelial layer is lost in carcinoma. P504S is abnormally expressed in high-grade PIN and prostate cancer epithelial cells, but is normally expressed in epithelial cells of the renal tubules, gall bladder and bronchi, and in hepatocytes.

**Useful For:** Aids in the identification of high-grade prostatic intraepithelial neoplasia and prostate cancer

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:
<0.35 kU/L

PINE 82381
Pine Nut, IgE
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


FPIAP 57670
Pineapple IgG
Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

Reference Values:
The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Pineapple, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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**Pinworm Exam, Perianal**

**Clinical Information:** Enterobius vermicularis (pinworms) are nematodes (roundworms) which are...
found worldwide in both temperate and tropical areas. The adults reside in the upper large intestine of humans and transmission is by the fecal-oral route. Adult females migrate to the perianal area, especially during the night, and deposit large numbers of eggs. Pinworm infection is the most common helminth infection in the United States and is the most common in young school-age children of all social classes. Pinworms do not produce significant intestinal disease but can cause irritating pruritus in the perianal area. They have also been implicated in vulvovaginitis in pre-pubertal girls and possibly in urinary tract infections. Several agents are effective in treating pinworm infection (pyrantel pamoate, mebendazole), and good personal hygiene will prevent transmission of the eggs.

**Useful For:** Detection of the eggs of Enterobius vermicularis on the skin of the perianal folds

**Interpretation:** Positive results are provided indicating the presence of eggs of Enterobius vermicularis.

**Reference Values:**
Negative (reported as positive or negative)

**Clinical References:**

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**Pipecolic Acid, Serum**

**Clinical Information:** Pipecolic acid (PA) is an intermediate of lysine metabolism and is oxidized in the peroxisomes by the enzyme L-pipecolate oxidase. In peroxisome biogenesis disorders (eg, Zellweger syndrome), the activity of this enzyme is lost, resulting in an increase in pipecolic acid levels. In contrast, in peroxisomal disorders involving single enzyme deficiencies such as D-bifunctional protein deficiency, PA is not elevated; therefore PA analysis is useful for differentiating between these 2 groups of disorders. Increased pipecolic acid levels may also be seen in alpha-aminoadipic semialdehyde dehydrogenase deficiency (pyridoxine-dependent epilepsy), hyperlysinemia types 1 and 2, and defects in proline metabolism. Theoretically, a defect in L-pipecolate oxidase can exist and several cases of hyperpipecolic acidemia have been reported, but a specific enzyme deficiency has not been described in any of the patients.

**Useful For:** Differentiating between disorders of peroxisomal biogenesis (eg, Zellweger syndrome) and disorders with loss of a single peroxisomal function Detecting abnormal elevations of pipecolic acid in serum

**Interpretation:** Elevated pipecolic acid levels are seen in disorders of peroxisomal biogenesis; normal levels are seen in disorders with loss of a single peroxisomal function. Abnormal levels of pipecolic acid should be interpreted together with the results of other biochemical markers of peroxisomal disorders, such as plasma C22-C26 very long-chain fatty acids, phytic acid, and pristanic acid (POX / Fatty Acid Profile, Peroxisomal [C22-C26], Serum); RBC plasmalogens; and bile acid intermediates.

**Reference Values:**
- <6 months: < or =6.0 nmol/mL
- 6 months-<1 year: < or =5.9 nmol/mL
- 1-17 years: < or =4.3 nmol/mL
- > or =18 years: < or =7.4 nmol/mL

**Clinical References:**

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 1812
Pipecolic Acid, Urine

**Clinical Information:** Pipecolic acid (PA) is an intermediate of lysine metabolism and is oxidized in the peroxisomes by the enzyme L-pipecolate oxidase. In peroxisome biogenesis disorders (eg, Zellweger syndrome), the activity of this enzyme is lost, resulting in an increase in pipecolic acid levels. In contrast, in peroxisomal disorders involving single enzyme deficiencies such as D-bifunctional protein deficiency, PA is not elevated; therefore PA analysis is useful for differentiating between these 2 groups of disorders. Increased pipecolic acid levels may also be seen in alpha-aminoadipic semialdehyde dehydrogenase deficiency (pyridoxine dependent epilepsy), hyperlysinemia types 1 and 2, and defects in proline metabolism. Theoretically, a defect in L-pipecolate oxidase can exist and several cases of hyperpipecolic acidemia have been reported, but a specific enzyme deficiency has not been described in any of the patients.

**Useful For:** Differentiating between disorders of peroxisomal biogenesis (eg, Zellweger syndrome) and disorders with loss of a single peroxisomal function Detecting abnormal elevations of pipecolic acid in urine

**Interpretation:** Elevated pipecolic acid levels are seen in disorders of peroxisomal biogenesis; normal levels are seen in disorders with loss of a single peroxisomal function. Abnormal levels of pipecolic acid should be interpreted together with the results of other biochemical markers of peroxisomal disorders, such as plasma C22-C26 very long-chain fatty acids, phytanic acid, pristanic acid (POX / Fatty Acid Profile, Peroxisomal [C22-C26], Serum); RBC plasmalogens; and bile acid intermediates.

**Reference Values:**
- < or =31 days: < or =223.8 nmol/mg creatinine
- 32 days-5 months: < or =123.1 nmol/mg creatinine
- 6 months-11 months: < or =45.0 nmol/mg creatinine
- > or =1 year: < or =5.7 nmol/mg creatinine

**Clinical References:**

Pistachio, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to
sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
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Reference values apply to all ages.


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**PIT1**

**PIT-1 Immunostain, Technical Component Only**

**Clinical Information:** Pit-1, also known as POU1F1, is a transcription factor involved in the development of the anterior pituitary and is useful in the classification of pituitary adenomas. Expression of Pit-1 is observed in somatotropic hormone-producing tumors (prolactin, growth hormone, or thyroid-stimulating hormone).

**Useful For:** Classification of pituitary adenomas

**Interpretation:** The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.

**Reference Values:** NA

**Pityrosporum orbiculare, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Placental Alkaline Phosphatase (PLAP) Immunostain, Technical Component Only**

**Clinical Information:** Placental alkaline phosphatase (PLAP) is expressed in cytotrophoblasts, syncytiotrophoblasts, and intermediate trophoblast cells. PLAP has been shown to be positive in various tumors, particularly germ-cell tumors and adenocarcinomas. PLAP expression has been described in tumors of Mullerian derivation, pulmonary and colonic carcinomas, and renal cell carcinomas.

**Useful For:** Aids in the identification of germ cell tumors
**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

### **PLAI**

**Plaice, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Plasma Cell Assessment, Blood**

**Clinical Information:** Plasma cell proliferative disorders are a group of hematologic neoplasms, all of which are derived from clonal plasma cells. These disorders exhibit a wide range of biologic activity ranging from monoclonal gammopathy of uncertain significance (MGUS), a usually indolent disorder with a low rate of disease progression, to multiple myeloma, a disease that most often is aggressive with poor long-term survival. Detecting plasma cell immunoglobulin (Ig) light chain restriction (ie, the presence of either predominately kappa or predominately lambda light chains) is an important element in assessing plasma cell clonality and, hence, establishing the diagnosis. Furthermore, a greater degree of peripheral blood involvement by these disorders is associated with more aggressive disease types and, therefore, is an adverse prognostic indicator. Flow cytometric immunophenotyping (FCIP) is a recognized method for detecting plasma cell Ig light chain restriction. However, shortcomings of this technique, as traditionally performed, include its relative insensitivity and its consistent underestimation of the number of clonal plasma cells present. Both of these short-comings are likely attributable to limitations of the instruments and antibodies used, as well as the presence of intracellular phenotypic heterogeneity, which created difficulties in accurately detecting and enumerating all of the clonal plasma cells. For this reason, the FCIP plasma cell clonality assessment previously performed in our laboratory was supplemented with a slide-based immunofluorescence technique. However, recent advances in flow cytometry have led to the development of more powerful instruments and antibody reagents that allow for the use of greater antibody combinations and increased resolution of the data. With these tools, the ability of FCIP to detect and enumerate plasma cell clones has been greatly enhanced, allowing us to discontinue the supplemental, labor-intensive, slide-based plasma cell evaluation in peripheral blood specimens. The following algorithms are available in Special Instructions: -Laboratory Screening Tests for Suspected Multiple Myeloma -Laboratory Approach to the Diagnosis of Amyloidosis

**Useful For:** Detecting peripheral blood involvement by plasma cell proliferative disorders
Establishing the diagnosis of and determining prognosis for plasma cell proliferative disorders

**Interpretation:** In normal peripheral blood specimens, no clonal plasma cells are present (polytypic or too few to detect). Plasma cells are CD38 and CD138 positive. Normal (polyclonal, nonneoplastic) plasma cells are typically CD19-positive, whereas neoplastic (clonal) plasma cells typically are CD19-negative. CD19 expression is especially helpful in distinguishing clonal from nonclonal plasma cells when few analyzable cells are present. CD45 may be expressed by both normal and neoplastic plasma cells. In some plasma cell proliferative disorders there are both CD45-positive and CD45-negative subsets within the clonal cell population. The evaluation of these antigens aids in the identification of abnormal plasma cells, however, they will not be reported independently.

**Reference Values:**
CD38+/CD138+ plasma cells = 0.0


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**Plasma Cell DNA Content and Proliferation, Bone Marrow**

**Clinical Information:** Plasma cell proliferative disorders are a group of plasma cell derived clonal hematologic neoplasms that exhibit a wide range of biologic activity ranging from monoclonal gammopathy of uncertain significance (MGUS), a usually indolent disorder with a low rate of disease progression, to multiple myeloma (MM), a disease that is often aggressive with poor long-term survival.
Detecting plasma cell clonality through demonstrating immunoglobulin (Ig) light chain restriction (ie, the presence of either predominately kappa or predominately lambda light chains), supplemented by the plasma cell immunophenotype and DNA index, is an important element in establishing the diagnosis. It is important to correctly classify patients with plasma cell proliferative disorders as the various disease entities are treated differently. A number of factors are used for this classification including the proportions of clonal bone marrow plasma cells, the DNA index of the clonal plasma cells, and their proliferative activity. The plasma cell DNA index and proliferation assessment by flow cytometry are rapid and reliable. This information can be used to distinguish patients with overt active MM from less aggressive diseases such as MGUS and smoldering MM. Furthermore, in combination with other laboratory data, the results of these studies can be used as a measure of disease aggressiveness in newly diagnosed MM and also to determine therapeutic efficacy and detect disease relapse in treated MM patients. See Laboratory Screening Tests for Suspected Multiple Myeloma in Special Instructions.

**Useful For:** Establishing a diagnosis of a plasma cell proliferative disorder Providing prognostic information for newly diagnosed multiple myeloma and other plasma cell proliferative disorders Assessing response to therapy and detecting disease relapse and progression in treated plasma cell proliferative disorder patients Determining plasma cell DNA content and proliferation

**Interpretation:** Plasma Cell Clonality: Plasma cell populations with a kappa to lambda ratio of either greater than 3.9 or less than 0.5 will be considered either kappa or lambda immunoglobulin light chain restricted (monotypic), respectively. As, in rare instances, immunoglobulin light chain restricted plasma cell populations may be polyclonal at the genetic level, the term monotypic rather than monoclonal plasma cells will be used. In addition to immunoglobulin light chain expression, other data collected will be used to supplement the detection of abnormal plasma cell populations. In plasma cells, CD19 expression is associated with the presence of benign, polytypic cell populations. Therefore CD19 expression will be used as a secondary element in detecting clonal plasma cells. While loss of plasma cell CD45 expression is associated with neoplasia, CD45 is expressed by both normal and neoplastic plasma cells. Therefore, absence of plasma cell CD45 expression will be used as an aid in detecting abnormal plasma cells. In some plasma cell proliferative disorders there are both CD45-positive and CD45-negative subsets within the clonal cell population, therefore inclusion of antibodies to this antigen allows for more sensitive detection of both subtypes. In addition, as DNA content will be simultaneously assessed, the detection of plasma cell aneuploidy will also serve as a tool for identifying abnormal plasma cell populations. These additional phenotypic tools for identifying abnormal plasma cells will increase the sensitivity of the method beyond examining light chain expression; particularly in biclonal plasma cell proliferative disorders in which there are both kappa and lambda immunoglobulin light chain expressing subsets. Plasma Cell Proliferation: The proportion of plasma cells in S-phase will be determined by measuring the proportion of cells with DNA content between the G0/G1 and G2/M peaks. In some instances, plasma cell proliferation will not be able to be determined by this method, including when there are fewer than 300 abnormal plasma cell events and when there are multiple aneuploid plasma cell populations. In newly diagnosed multiple myeloma, a plasma cell labeling index (PCLI) of greater than or equal to 3.0 is associated with a more aggressive disease course.(1,2) As there was a 100% concordance between a PCLI of greater than 3.0 and an estimated S-phase of greater than 1.5%, and this value is published standard for identifying plasma cell neoplasms with a high proliferative rate, it will be noted in the report if the estimated S-phase exceeds this value.(3,4) DNA Index: Processed cells are stained with DAPI to determine the DNA index of the abnormal plasma cells. This will be determined by dividing the measured DNA content of the G0/G1 abnormal plasma cells by the DNA content of the normal G0/G1 plasma cells present. For this determination, normal plasma cells are the optimal control cell population due to similarities in nuclear and overall cell size. Plasma cells with a G0/G1 DNA content index of less than 0.95 will be considered hypodiploid (worst prognosis); those with a G0/G1 DNA content index of greater than 1.05 will be considered hyperdiploid (favorable prognosis). Plasma cells with a DNA index of 1.9 to 2.1 will be considered tetraploid (nonfavorable prognosis) if a confirmatory G2/M population with a DNA index of 4 is identified. As noted above, since normal plasma cells are neither hyper- nor hypodiploid, DNA index will be used as a supplemental tool in detecting clonal plasma cells. Percent Polyclonal Plasma Cells in Total Plasma Cells: It has been shown that higher percent polyclonal plasma cells in total plasma cells can mean longer progression-free survival, higher response rates, and lower frequency of high-risk cytogenetics abnormalities. Studies have also shown a higher incidence of polyploid plasma cells in monoclonal gammopathy of uncertain significance and smoldering myeloma in comparison to multiple myeloma.
Plasma Cell Proliferative Disorder (PCPD), FISH

Clinical Information: Multiple myeloma is a hematologic neoplasm that generally originates in the bone marrow and develops from malignant plasma cells. There are 4 main categories of plasma cell proliferative disorders (PCPD): asymptomatic myeloma, smoldering myeloma, indolent myeloma, and multiple myeloma. Asymptomatic myeloma patients have nonspecific symptoms that may be attributed to other diseases. Generalized bone pain, anemia, numbness or limb weakness, symptoms of hypercalcemia, and recurrent infections are all symptoms that may indicate myeloma. In smoldering myeloma there is a monoclonal protein spike, but it is stable. Indolent myeloma is a slowly progressing myeloma. As myeloma progresses, the malignant plasma cells interfere with normal blood product formation in the bone marrow resulting in anemia and leukopenia. Myeloma also causes an overstimulation of osteoclasts, causing excessive breakdown of bone tissue without the normal corresponding bone formation. These bone lesions are seen in approximately 66% of myeloma patients. In advanced disease, bone loss may reach a degree where the patient suffers fractures easily. Multiple myeloma is increasingly recognized as a disease characterized by marked cytogenetic, molecular, and proliferative heterogeneity. This heterogeneity is manifested clinically by varying degrees of disease aggressiveness. Multiple myeloma patients with more aggressive disease experience suboptimal responses to some therapeutic approaches; therefore, identifying these patients is critically important for selecting appropriate treatment options.

Useful For: Aiding in the diagnosis of new cases of multiple myeloma or other plasma cell proliferative disorders Identifying prognostic markers based on the anomalies found

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe.

Reference Values: An interpretive report will be provided.

**Plasma Cell Proliferative Disorder, FISH, Tissue**

**Clinical Information:** A plasmacytoma is a localized proliferation of plasma cells that are cytologically and immunophenotypically identical to the plasma cell clones seen in myeloma. There are 2 primary types of plasmacytomas: solitary plasmacytoma of bone (SPB) and extramedullary plasmacytoma (EP). SPBs are a localized bone tumor comprised of plasma cells and account for about 5% of all plasma cell neoplasms. Common sites for SPBs are the vertebrae, ribs, skull, pelvis, femur, clavicle, and scapula. Patients often present with pathological fracture and/or bone pain near the lesion. Treatment is typically radiation therapy; at 10 years, 35% of patients appear to be cured, 55% develop myeloma, and 10% have local recurrence. EPs are tumors of plasma cells that form in areas away from the bone and account for 3% to 5% of all plasma cell neoplasms. Approximately 80% of EPs occur in the upper respiratory tract. Less common locations include the gastrointestinal tract, bladder, testis, central nervous system, and skin. Treatment consists of radiation therapy. Regional recurrence develops in about 25% of patients, but development of myeloma is less frequent, occurring in only about 15% of patients. Genetics of both types of plasmacytomas, while not extensively studied, appears to be the same as plasma cell myeloma.

**Useful For:** Supporting the diagnosis of plasmacytoma when coordinated with a surgical pathology consultation

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for a given probe set. A positive result supports the diagnosis of a plasmacytoma. A negative result does not exclude the diagnosis of a plasmacytoma.

**Reference Values:**

An interpretive report will be provided.

**Clinical References:**

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**Plasma Hemoglobin, Plasma**

**Clinical Information:** Hemoglobin is contained within erythrocytes and significant amounts of "free hemoglobin" (outside the RBC) is not present in plasma in normal states. This free hemoglobin is also called plasma hemoglobin. Normal blood draw procedures cause a limited degree of unavoidable disruption and therefore a small amount of free hemoglobin may be present in normal people. When detectable, the total plasma hemoglobin and a subcomponent, oxyhemoglobin, are both reported. Significant amounts of free hemoglobin occur in plasma following disruption of the RBC for any reason. This might result from a transfusion reaction or mechanical fragmentation of red blood cells due to instrumentation, surgical procedures, or mechanical devices. Patients requiring support from extracorporeal membrane oxygenation (ECMO) or centrifugal ventricular assist devices (cVAD) are commonly monitored for trends in plasma free hemoglobin levels to assess for increasing hemolysis. Sharp spikes in plasma hemoglobin levels can indicate pump disruption. However, plasma hemoglobin can be artifactually increased due to a traumatic blood draw or prolonged exposure to post-draw red blood cells. Additionally, bilirubin interferes substantially with the ability to calculate total plasma hemoglobin levels and results in spurious and unreliable results. This is a difficulty frequently encountered in serially tested patients. When this occurs, the oxyhemoglobin level tends to show less interference and will be the only analyte reported in the presence of increased bilirubin (>5 mg/dL). When using trending data, total plasma hemoglobin and oxyhemoglobin levels are not interchangeable and should be compared within their subgroups only.

**Useful For:** Determining whether hemolysis is occurring such as from:

- Transfusion reaction
-Mechanical fragmentation of red blood cells -Relative comparison to baseline levels in extracorporeal membrane oxygenation (ECMO) and centrifugal ventricular assist device (cVAD) patients to assess pump disruption

**Interpretation:** An elevation in plasma hemoglobin above the reference range indicates likely intravascular hemolysis due to one of the causes listed above.

**Reference Values:**

**TOTAL HEMOGLOBIN**

- or =12 months: 0.0-15.2 mg/dL  
Reference values have not been established for patients who are <12 months of age.

**OXYHEMOGLOBIN**

- or =12 months: 0.0-12.4 mg/dL  
Reference values have not been established for patients who are <12 months of age.


### PAI1

**86083**

**Plasminogen Activator Inhibitor Antigen, Plasma**

**Clinical Information:** Plasminogen activator inhibitor type 1 (PAI-1) antigen is a single-chain glycoprotein (MW 50,000) produced by endothelial cells and hepatocytes and is also present in alpha granules of platelets. PAI-1 is a serine protein inhibitor that is secreted in response to inflammatory reactions. Platelet alpha granules contain large amounts of PAI-1, which is released during vascular injury and assists in fibrin clot stability. PAI-1 is synthesized in the active form but has marked functional instability and a functional half-life of about 2 hours in vivo. Circulating PAI-1 is bound to vitronectin, which protects the inhibitor from inactivation and may assist in targeting the inhibitor to sites of vascular injury. At least 4 different conformations of PAI-1 have been described: 1) the active form that reacts with plasminogen activator; 2) a latent form that is nonreactive; 3) a substrate form that can be cleaved by plasminogen activators but is noninhibitory; and 4) the inert form of PAI-1 generated by the cleavage of the reactive site. PAI-1 is the main inhibitor of tissue-type plasminogen activator (tPA) and urokinase plasminogen activator (uPA) and, as such, plays an important role in the regulation of fibrinolysis. Elevated levels of PAI-1 result in deficient plasminogen activation and are associated with a predisposition to thrombosis, including veno-occlusive disease (VOD) after bone marrow transplantation (BMT). Primary injury to the hepatic sinusoidal endothelium and hepatocytes induced by high-dose chemoradiotherapy is believed to be the key event in the pathogenesis of VOD. The clinical diagnosis of VOD is complex because the clinical signs and symptoms can occur as a result of other processes that can complicate the posttransplant period such as sepsis, graft-versus-host disease (GVHD), cyclosporine toxicity, other medications, hemolysis, or parenteral nutrition. Liver biopsy, although safer since the widespread introduction of transjugular procedures, remains hazardous in this thrombocytopenic population. A sensitive and specific assay would be invaluable in guiding management and avoiding potentially hazardous invasive diagnostic procedures. Along these lines several investigators have studied various markers of hypercoagulability for possible pathogenic and predictive relevance. Aside from serum bilirubin level, no laboratory marker has been standardized as a diagnostic marker of VOD and the severity of VOD remains retrospectively defined. Lee et al analyzed 115 patients after allogenic BMT in an attempt to identify diagnostic and severity markers of VOD. Of the 115 patients, 50 developed VOD. (1) Multiple logistic regression models were constructed that included recognized relevant clinical and hemostatic variables. Of the hemostatic variables, only PAI-1 antigen was identified as an independent marker for the occurrence of VOD. This confirmed findings of an earlier, smaller study, that PAI-1 is a powerful diagnostic marker of VOD during the early period post-BMT, and can distinguish VOD from other causes of hyperbilirubinemia post-BMT such as GVHD and drug toxicity. Furthermore, PAI-1 antigen and bilirubin were independent variables for
predicting severe VOD. Familial thrombosis has been associated with inherited elevation of plasma PAI-1 activity. Increased levels of PAI-1 have also been reported in a number of conditions including malignancy, liver disease, the postoperative period, septic shock, the second and third trimesters of pregnancy, obesity, and coronary heart disease. Low plasma levels of the active form of PAI-1 have been associated with abnormal, clinically significant bleeding. Complete deficiency of PAI-1, either congenital or acquired, is associated with bleeding manifestations that include hemarthroses, hematomas, menorrhagia, easy bruisings, and postoperative hemorrhage.

**Useful For:** Identification of heredity elevation or deficiency of plasminogen activator inhibitor type 1
Determination of risk for veno-occlusive disease associated with bone marrow transplantation Differential diagnosis of impaired fibrinolysis Prognostic marker of occurrence or recurrence of thrombosis

**Interpretation:** Increased levels of plasminogen activator inhibitor type 1 (PAI-1) are associated with a predisposition to thrombosis. Decreased or absent levels of detectable functional PAI-1 will result in a life-long bleeding diathesis.

**Reference Values:**

3-72 ng/mL

**Clinical References:**

**FPAIG**

Plasminogen Activator Inhibitor-1, 4G/5G Genotyping (PAI-1 Polymorphism)

**Clinical Information:** The PAI-1 4G allele is an inherited characteristic. If the polymorphism is present in a heterozygous or homozygous fashion, we recommend that the patient and their family consider genetic counseling to obtain additional information on inheritance and to identify other family members at risk. If a patient possesses two or more congenital or acquired risk factors, the risk of disease may rise to more than the sum of the risk ratios for the individual risk factors. For instance, a combination of the 4G/4G genotype and the insulin resistance syndrome may confer an increase in cardiovascular disease risk over that conferred by the presence of an isolated PAI-1 4G/4G polymorphism.


**PSGN**

Plasminogen Activity, Plasma

**Clinical Information:** During the formation of a hemostatic (fibrin) plug, biochemical mechanisms are initiated to limit the extent of the hemostatic process at the site of injury and maintain vascular patency. This process of fibrinolysis is defined as the plasmin-mediated degradation of fibrin. Plasmin limits the extent of the hemostatic process at the site of vessel injury. Plasmin is generated from its precursor, plasminogen, by plasminogen activators (ie, tissue plasminogen-activator: tPa; urokinase-type
Plasminogen is a single-chain glycoprotein that is synthesized in the liver and has a biologic half-life of approximately 2 days. (1) Deficiency of plasminogen may be inherited or acquired. Persons with congenital plasminogen deficiency are at an increased risk for development of an ocular condition called ligneous conjunctivitis. Congenital deficiency of plasminogen is autosomal transmitted and rare in the general population, with a prevalence of approximately 0.4%. (2) Based on the results of functional and immunologic (antigenic) assays, 2 types of plasminogen deficiency have been identified: -Quantitative deficiency (type I) -defined by a corresponding decrease in both plasminogen activity and antigen level -Functional deficiency (type II) -caused by a normally synthesized but dysfunctional plasminogen This plasminogen activity assay will identify both types of deficiency. Acquired causes of plasminogen deficiency include consumption such as with thrombolytic therapy (urokinase, tPA) or disseminated intravascular coagulation and fibrinolysis (DIC/ICF), or decreased synthesis (liver disease). (1)

**Useful For:** Evaluating patients with ligneous conjunctivitis (strong association with homozygous plasminogen deficiency) Evaluating fibrinolysis, in combination with other components of the fibrinolytic system (fibrinogen, tissue plasminogen-activator-inhibitor, and d-dimers)

**Interpretation:** Plasminogen activity below 75% may represent a congenital deficiency state, if acquired deficiency can be excluded. Hereditary abnormalities of plasminogen (deficiency or dysfunction) are very uncommon. Acquired causes of plasminogen deficiency are much more common and may be the result of consumption due to thrombolytic therapy or intravascular coagulation and fibrinolysis or decreased synthesis (ie, liver disease). Plasminogen levels are low at birth (approximately 50% of adult normal level) and reach adult levels at 6 months of age.

**Reference Values:**
75-140%

**Clinical References:**

**Platelet Antibodies, Indirect (IgG, IgM, IgA)**

**Interpretation:** Circulating antibodies to platelets, detected by Flow Cytometry, are found in the sera of patients with immune mediated disorders. Platelet antibodies have been associated with ITP and drug-induced thrombocytopenia.

**Reference Values:**
Platelet Ab, Indirect (IgG): Negative
Platelet Ab, Indirect (IgM): Negative
Platelet Ab, Indirect (IgA): Negative

**Platelet Antibody Screen, Serum**

**Clinical Information:** Platelet antibodies may be allo- or autoantibodies and may be directed to a wide range of antigenic “targets” carried on platelet cytoplasmic membranes. Serum platelet antibody test is optimized to identify the presence of platelet allo-antibodies in the patient. Platelet alloantibodies are involved in several clinical situations such as: -Immune mediated refractoriness to platelet transfusions usually due to antibodies to HLA class I and sometimes to antibodies specific to platelet antigens. -Neonatal alloimmune thrombocytopenia (NAIT) -Posttransfusion purpura (PTP), which are usually associated with platelet-specific antibodies This test is not recommended for the diagnosis of immune thrombocytopenia (ITP) or autoimmune thrombocytopenia. Tests that are optimized to detect antibodies bound to the platelets will be useful in these situations; cell-bound platelet antibody (Direct) test is strongly recommended instead (CBPAN / Cell Bound Platelet Auto-Antibody Screen, Blood).
**Useful For:** Detecting alloantibodies to epitopes on platelet glycoproteins IIb/IIIa, Ib/IX, Ia/IIa, IV and HLA Class I antigens to evaluate cases of immune mediated refractoriness to platelet transfusions, posttransfusion purpura, or neonatal alloimmune thrombocytopenia

**Reference Values:**
Not applicable

**Clinical References:**

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**Platelet Surface Glycoprotein by Flow Cytometry, Blood**

**Clinical Information:** Platelets have essential roles in primary hemostasis. Exposed collagen at a vascular damage site can activate platelets via collagen receptor GPVI and GPIa and bind shear-stretched multimeric VWF proteins, which subsequently interact with the platelet surface receptor, GPIb-V-IX. Upon full activation, platelets can aggregate by binding to fibrinogen through activated GPIb-GPIIa receptors. Deficiency of platelet surface glycoproteins can cause bleeding diathesis. Platelet flow cytometric analysis is the preferred method to assess hereditary platelet disorders due to quantitative surface glycoprotein (GP) deficiencies. GP expression levels can be measured by using fluorescent-conjugated GP-specific antibodies and their fluorescent intensities can be compared to normal ranges of various glycoproteins. CD Number Glycoprotein Name Integrin Name CD41 GPIIb Alpha 2b CD42a GPIX NA CD42b GPIb-alpha NA CD49b GPIa Alpha 2 CD61 GPIIIa Beta 3 NA GPVI NA

**Useful For:** Identification of markedly decreased CD41 (GPIIb) and CD61 (GPIIIa) expression levels, which are diagnostic for Glanzmann thrombasthenia Identification of markedly decreased CD42a (GPIX) and CD42b (GPIb-alpha) expression levels, which are diagnostic for Bernard-Soulier syndrome Identification of decreased GPVI expression, which suggests collagen receptor deficiency Identification of decreased CD49b (GPIa), which suggests collagen receptor deficiency

**Interpretation:** CD Markers % Reference Range Median Comments CD41 and CD61 50%-69% (Marginally) Marginally decreased platelet surface receptors CD41 (GPIIb) and CD61 (GPIIIa) are of uncertain clinical significance. This finding could be a laboratory artifact due to suboptimal sample condition, benign polymorphisms, or a heterozygous state of Glanzmann thrombasthenia. Recommend correlation with patient’s clinical findings and results of platelet functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if clinically indicated. 30%-50%: (Moderately) <30%: (Markedly) Platelet surface expression of CD41 (GPIIb) and CD61 (GPIIIa) are moderately or markedly decreased. This finding is suggestive for a variant of Glanzmann thrombasthenia. Recommend correlation with patient's clinical findings and results of platelet functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if clinically indicated. CD42a and CD42b 50%-69% (Marginally) Marginally decreased platelet surface receptors CD42a (GPIX) and CD42b (GPIb-alpha) are of uncertain clinical significance. This finding could be a laboratory artifact due to suboptimal sample condition, benign polymorphisms, or a heterozygous state of Bernard-Soulier syndrome. Recommend correlation with patient’s clinical findings and results of platelet functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if clinically indicated.
functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if clinically indicated. CD49b 30%-59% (Marginally) Marginally decreased platelet surface receptor CD49b (GPIa) is of uncertain clinical significance. This finding could be a laboratory artifact due to suboptimal sample condition, a benign polymorphism, or a variant of platelet collagen receptor glycoprotein Ia/IIa deficiency. Recommend correlation with patient's clinical findings and results of platelet functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if clinically indicated. 10%-30% (moderately) <10% (Markedly) Platelet surface expression of CD49b (GPIa) is moderately or markedly decreased. This finding is suggestive for a variant of a variant of platelet collagen receptor glycoprotein Ia/IIa deficiency. Recommend correlation with patient's clinical findings and results of platelet functional studies, and consider repeating platelet glycoprotein profile studies by flow cytometry to verify the present finding if clinically indicated. GPIIIa CD61: > or =70.0% (Normal Range-Median) GPA IIb CD41: > or =70.0% (Normal Range-Median) GPA IIbo CD42a: > or =70.0% (Normal Range-Median) GPA IIIa CD61: > or =70.0% (Normal Range-Median) GPA IIb CD41: > or =70.0% (Normal Range-Median) GPA IIIa CD61: > or =70.0% (Normal Range-Median) GPVI CD49b: > or =60.0% (Normal Range-Median) GPX CD42a: > or =70.0% (Normal Range-Median) GPb-alpha CD42b: > or =70.0% (Normal Range-Median) GPIa CD49b: > or =60.0% (Normal Range-Median) GPX CD42a: > or =70.0% (Normal Range-Median) GPb-alpha CD42b: > or =70.0% (Normal Range-Median) GPIa CD49b: > or =60.0% (Normal Range-Median)

Reference Values:

GPIIb CD41: > or =70.0% (Normal Range-Median)
GPIIIa CD61: > or =70.0% (Normal Range-Median)
GPIX CD42a: > or =70.0% (Normal Range-Median)
GPIIb-alpha CD42b: > or =70.0% (Normal Range-Median)
GPIa CD49b: > or =60.0% (Normal Range-Median)

Clinical References:


Platelet Transmission Electron Microscopic Study

Clinical Information: Patients with either hereditary or acquired platelet disorders usually have bleeding diathesis, which can potentially be life threatening. A reliable laboratory diagnosis of a platelet disorder can significantly impact patients' clinical management and outcome. Platelet transmission electron microscopy (PTEM) has been an essential tool for laboratory diagnosis of various hereditary platelet disorders since it was first used to visualize fibrin-platelet clot formation in 1955. PTEM employs 2 main methods to visualize platelet ultrastructure, whole mount (WM) TEM and thin section (TS) TEM. WM-TEM is considered the gold standard test for diagnosing dense granule deficiencies in Hermansky-Pudlak syndrome, alpha-delta platelet storage pool deficiency, Paris-Trousseau-Jacobsen syndrome, Wiskott-Aldrich syndrome, TAR (thrombocytopenia, absent radii) syndrome, Chediak-Higashi syndrome, and more. TS-TEM is a preferred method to visualize platelet alpha granules, other organelles and abnormal inclusions. Platelet disorders that can be detected by PTEM include (but are not limited to): Delta granules (dense bodies): -Hermansky Pudlak syndrome -Wiskott-Aldrich syndrome -Chediak Higashi syndrome -Jacobson syndrome -TAR platelet syndrome -White platelet syndrome -Storage pool deficiency, not otherwise specified Alpha granules: -Gray platelet syndrome -White platelet syndrome -Alpha-delta platelet syndrome -X-linked GATA 1 mutation -Jacobson syndrome -Paris-Trousseau syndrome -Alpha and delta granules: -Alpha-delta storage pool deficiency
Useful For: Diagnosing platelet disorders

Interpretation: Ultrastructural abnormalities identified by platelet transmission electron microscopy are evaluated by a Mayo hematopathologist. Platelet size, alpha granules, golgi complex, and abnormal inclusions will be assessed as part of the morphologic examination under transmission electron microscopy. Distinct and sometimes pathognomonic ultrastructural abnormalities are found in Hermansky Pudlak syndrome, gray platelet syndrome with virtually absent alpha granules, white platelet syndrome, Medich giant platelet disorder, X-linked GATA-1 macrothrombocytopenia, and, recently described, York platelet syndrome.

Reference Values:
Mean dense granules/platelet > or =1.2


Ptse

Platinum, Serum

Clinical Information: Cisplatin (cis-diamminedichloroplatinum)(1) and carboplatin (cyclobutanedicarboxylatoplatinum)(2,3) are used in cancer chemotherapy. Clinical trials demonstrate schedule-dependent activity of carboplatin in patients with relapsed and refractory acute leukemia. Patients responding to carboplatin therapy had peak serum platinum concentration in the range of 0.6 to 1.8 mcg/mL. Trough concentrations ranged from 0.1 to 0.4 mcg/mL. Platinum concentrations maintained >1.8 mcg/mL can induce neutropenia and renal failure if coadministered with nephrotoxic antibiotics.(1,2) Unexposed individuals should have platinum concentrations <0.04 mcg/mL.(4)

Useful For: Monitoring platinum levels in patients receiving cisplatin or other platinum-containing drugs

Interpretation: Effective Range: -Patients responding to carboplatin therapy had peak plasma platinum concentration in the range of 0.6 to 1.8 mcg/mL. -Trough concentrations range from 0.1 to 0.4 mcg/mL. -Platinum concentrations maintained >1.8 mcg/mL can induce neutropenia and renal failure if coadministered with nephrotoxic antibiotics. -Unexposed patients should have platinum concentrations <0.04 mcg/mL.

Reference Values:
Cisplatin Infusion, Peak: 0.6-1.8 mcg/mL
Cisplatin Infusion, Trough: 0.1-0.4 mcg/mL
Unexposed: <0.04 mcg/mL


Plazomicin, Plasma

Clinical Information: Plazomicin is an aminoglycoside engineered to overcome the most prevalent aminoglycoside-modifying enzymes, which are a common aminoglycoside-resistance mechanism. Plazomicin levels are intended to be used by clinicians to support clinical decision-making in guiding appropriate dosage adjustments for patients on plazomicin therapy. The safety and effectiveness of plazomicin treatment in an individual patient should ultimately be based on clinical response. The trough reference range represents plazomicin minimum (trough) concentrations associated with a reduced risk of nephrotoxicity. However, some patients with plasma trough concentrations outside the trough reference range.
range may achieve a satisfactory response.

**Useful For:** An aid to achieving the desired plasma concentrations of plazomicin

**Interpretation:** The plazomicin drug package insert should be consulted for information regarding the utilization of plazomicin concentrations and guidance for therapeutic drug monitoring (TDM). For patients with complicated urinary tract infections (cUTI) with creatinine clearance (CLcr) values of 15 and higher, but less than 90 mL/min, monitoring of plazomicin plasma trough concentrations is recommended to avoid potentially toxic levels. For this subset of patients, it is recommended that the sample for the plazomicin minimum (trough) concentration measurement be drawn within approximately 30 minutes before administration of the second dose of plazomicin. Plazomicin dosage should be adjusted to avoid trough levels above 3 mcg/mL. Modeled plazomicin trough concentrations from 377 patients with cUTI in Phase 2 and Phase 3 trials have been determined to range from 0.1 to 3.3 mcg/mL (5-95 percentile range) with a median and geometric mean of 0.8 and 0.7 mcg/mL, respectively. Measured plazomicin trough concentrations by liquid chromatography-tandem mass spectrometry (LC-MS/MS) for 274 trough samples in the Phase 3 Study ACHN-490-009 resulted in similar values (0.2 to 5.7 mcg/mL 5-95 percentile range; 1.1 mcg/mL median and geometric mean). For effective treatment, some patients may require plasma levels outside of these ranges. Therefore, the expected ranges are provided as guidelines, and individual patient results should be interpreted with the aid of the dosage adjustment algorithms in the plazomicin drug package insert and in the context of the patient's other clinical signs and symptoms.

**Reference Values:**

Complicated urinary tract infections (cUTI):

Trough Reference Range: <3 mcg/mL

(Trough=30 min before second dose, and 30 min before subsequent doses as appropriate)

**Clinical References:**


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**Plum, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
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<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
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<tr>
<td>2</td>
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<tr>
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</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**PML/RARA Quantitative, PCR**

**Clinical Information:** Acute promyelocytic leukemia (APL) accounts for 5% to 10% of acute myeloid leukemia, and generally has a good prognosis with current treatment protocols. APL cells contain a fusion gene comprised of the downstream sequences of the retinoic acid receptor alpha gene (RARA) fused to the promoter region and upstream sequences of one of several genes, the most common (>80%) being the promyelocytic leukemia gene (PML). The fusion gene is designated PML/RARA and may be seen in a karyotype as t(15;17)(q22;q12). Messenger RNA (PML/RARA) produced from the fusion gene can be detected using a PCR-based assay, and indicates the presence of neoplastic cells. The PCR-based assay has greater sensitivity than standard methods such as morphology review, karyotyping, or FISH. Recent studies have indicated that sensitive monitoring is important because the majority of patients who remain PCR positive, or become PCR positive again following treatment, will relapse and likely benefit from early intervention for residual/recurrent disease. This quantitative assay allows PML/RARA levels to be monitored rather than simply detecting the presence or absence of disease.

**Useful For:** Diagnosis of acute promyelocytic leukemia (APL) Detection of residual or recurrent APL Monitoring the level of promyelocytic leukemia/retinoic acid receptor alpha (PML/RARA) in APL patients

**Interpretation:** The assay is reported in the form of a normalized ratio of promyelocytic leukemia/retinoic acid receptor alpha (PML-RARA) fusion transcript to the control gene GusB expressed as a percentage, which is an estimate of the level of PML/RARA RNA present in the specimen, expressed in relation to the level of RNA from an internal control gene (beta glucuronidase, designated GUSB). The normalized ratio has no units but is directly related to the level of PML/RARA detected (ie, larger numbers indicate higher levels of PML/RARA and smaller numbers indicate lower levels). A relative expression value minimizes variability in the RNA levels measured in separate specimens tested at different times. Although a quantitative PCR assay is performed, the precision of the assay is such that results must be considered semiquantitative, and it is recommended that only log changes be considered significant. Critical results, such as a change in the status of positivity, should be repeated on a separate specimen to verify the result.

**Reference Values:** An interpretive report will be provided.
If positive, a value representing a ratio of PML-RARA fusion transcript to the control gene GusB expressed as a percentage will be reported.


**PMPDD 66569**

**PMP22 Gene, Large Deletion and Duplication Analysis**

**Clinical Information:** This test is appropriate for individuals with clinical features suggestive of Charcot-Marie-Tooth type 1A (CMT1A) and hereditary neuropathy with liability to pressure palsies (HNPP). CMT1A is a dominantly inherited disease characterized progressive distal muscle weakness and atrophy, sensory loss, and slow nerve conduction velocity starting early in life. Duplications of the PMP22 gene are associated with CMT1A. Deletions of PMP22 are associated with hereditary neuropathy with liability to pressure palsies (HNPP), a dominantly inherited disease resulting in peripheral neuronal demyelination. HNPP is characterized clinically by recurrent focal motor and sensory neuropathy in a single nerve that can manifest as numbness, muscular weakness, and atrophy.

**Useful For:** Diagnosis of Charcot-Marie-Tooth type 1A or hereditary neuropathy with liability to pressure palsies

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations. (1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.


**PMS2I 35525**

**PMS-2, Immunostain (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**PMS2Z 35528**

**PMS2 Gene, Full Gene Analysis**

**Clinical Information:** Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer or HNPCC) is an autosomal dominant hereditary cancer syndrome associated with germline mutations in the mismatch repair genes, MLH1, MSH2, MSH6, and PMS2. Deletions within the 3-prime end of the EPCAM gene have also been associated with Lynch syndrome, as this leads to inactivation of the MSH2 promoter. Lynch syndrome is predominantly characterized by significantly increased risks for colorectal and endometrial cancer. The lifetime risk for colorectal cancer is highly variable and dependent on the gene involved. The risk for colorectal cancer associated MLH1 and MSH2 mutations (approximately 50%-80%) is generally higher than the risks associated with mutations in the other Lynch syndrome-related genes, and the lifetime risk for endometrial cancer (approximately 25%-60%) is also highly variable. Other malignancies within the tumor spectrum include gastric cancer, ovarian
cancer, hepatobiliary and urinary tract carcinomas, and small bowel cancer. The lifetime risks for these cancers are <15%. Of the 4 mismatch repair genes, mutations within the PMS2 gene confer the lowest risk for any of the tumors within the Lynch syndrome spectrum. Several clinical variants of Lynch syndrome have been defined. These include Turcot syndrome, Muir-Torre syndrome, and homozygous mismatch repair mutations (also called constitutional mismatch repair deficiency syndrome). Turcot syndrome and Muir-Torre syndrome are associated with increased risks for cancers within the tumor spectrum described, but also include brain and central nervous system malignancies and sebaceous carcinomas, respectively. Homozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of Lynch syndrome. One such strategy involves testing the tumors from suspected individuals for microsatellite instability and/or immunohistochemistry for the presence or absence of defective DNA mismatch repair. Tumors that demonstrate absence of expression of PMS2 are more likely to have a germline mutation in the PMS2 gene.

**Useful For:** Establishing a diagnosis of Lynch syndrome/hereditary nonpolyposis colorectal cancer

Determining whether absence of PMS2 protein in tumor tissue, as demonstrated by immunohistochemistry, is associated with a germline mutation in the affected individual

Identification of familial PMS2 mutation to allow for predictive testing in family members

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**

An interpretative report will be provided.

sebaceous carcinomas, respectively. Homozygous or compound heterozygous mismatch repair mutations, characterized by the presence of biallelic deleterious mutations within a mismatch repair gene, are associated with a different clinical phenotype defined by hematologic and brain cancers, cafe au lait macules, and childhood colon or small bowel cancer. There are several strategies for evaluating individuals whose personal or family history of cancer is suggestive of HNPCC. Testing tumors from individuals at risk for HNPCC for microsatellite instability (MSI) indicates the presence or absence of defective DNA mismatch repair phenotype within the tumor, but does not suggest in which gene the abnormality rests. Tumors from individuals affected by HNPCC usually demonstrate an MSI-H phenotype (MSI >30% of microsatellites examined). The MSI-H phenotype can also be seen in individuals whose tumors have somatic MLH1 promoter hypermethylation. Tumors from individuals that show the MSS/MSI-L phenotype (MSI at <30% of microsatellites examined), are not likely to have HNPCC or somatic hypermethylation of MLH1. Immunohistochemistry (IHC) is a complementary testing strategy to MSI testing. In addition to identifying tumors with defective DNA mismatch repair, IHC analysis is helpful for identifying the gene responsible for the defective DNA mismatch repair within the tumor, because the majority of MSI-H tumors show a loss of expression of at least 1 of the 4 mismatch repair genes described above. Testing is typically first performed on the tumor of an affected individual and in the context of other risk factors, such as young age at diagnosis or a strong family history of HNPCC-related cancers. If defective DNA mismatch repair is identified within the tumor, mutation analysis of the associated gene can be performed to identify the causative germline mutation and allow for predictive testing of at-risk individuals. Of note, MSI-H phenotypes and loss of protein expression by IHC have also been demonstrated in various sporadic cancers, including those of the colon and endometrium. Absence of MLH1 and PMS2 protein expression within a tumor, for instance, is most often associated with a somatic alteration in individuals with an older age of onset of cancer than typical HNPCC families. Therefore, an MSI-H phenotype or loss of protein expression by IHC within a tumor does not distinguish between somatic and germline mutations. Genetic testing of the gene indicated by IHC analysis can help to distinguish between these 2 possibilities. In addition, when absence of MLH1/PMS2 is observed, BRMLH / MLH1 Hypermethylation and BRAF Mutation Analyses, Tumor or ML1HM / MLH1 Hypermethylation Analysis, Tumor may also help to distinguish between a sporadic and germline etiology. It should be noted that this HNPCC screen is not a genetic test, but rather stratifies the risk of having an inherited cancer predisposition syndrome, and identifies patients who might benefit from subsequent genetic testing.

**Useful For:** Evaluation of tumor tissue to identify patients at high risk for having hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome Evaluation of tumor tissue to identify patients at risk for having hereditary endometrial carcinoma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**


**FPNAP**

57589

**Pneumococcal Antibody Panel (12 Serotype)**

**Reference Values:**

<table>
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<th>Reference Range</th>
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<tr>
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</tr>
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</table>

**PNRP**

81698

**Pneumocystis jiroveci, Molecular Detection, PCR**

**Clinical Information:** Pneumocystis pneumonia is an important cause of opportunistic infection in immunocompromised patients, particularly those with HIV. The causative agent, Pneumocystis jiroveci, cannot be cultured in vitro and, therefore, laboratory detection has historically relied upon microscopic identification directly from patient specimens using fluorescent stains or antibodies. Unfortunately, stains often lack sensitivity and require expertise on the part of the reader in order to differentiate Pneumocystis jiroveci from staining artifacts and other fungi. This real-time PCR assay provides sensitive (21% more sensitive than direct detection using fluorescent calcofluor white stain), specific, and objective detection of Pneumocystis from bronchoalveolar lavage fluid and other specimens.

**Useful For:** Preferred test for detection of Pneumocystis

**Interpretation:** A positive result indicates the presence of Pneumocystis DNA. A negative result indicates the absence of detectable Pneumocystis DNA.

**Reference Values:**

Not applicable

**Clinical References:**

Clinical Information: Pneumocystis jiroveci is one of the major microbial pathogens associated with opportunistic pulmonary infections in patients receiving immunosuppressive therapy or with immune deficiencies. Presently, the most common means to diagnose Pneumocystis jiroveci infection is by microscopic detection of the organisms in specimens such as bronchoalveolar lavage, open lung biopsy tissue, induced sputum and transtracheal aspirate.

Useful For: Diagnosis of Pneumocystis jiroveci pneumonia

Interpretation: Negative: no cysts observed Positive: cysts present

Reference Values:


PNH, PI-Linked Antigen, Blood

Clinical Information: Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematologic disorder characterized by nocturnal hemoglobinuria, chronic hemolytic anemia, thrombosis, pancytopenia, and, in some patients, acute or chronic myeloid malignancies. PNH appears to be a hematopoietic stem cell disorder that affects erythroid, granulocytic, and megakaryocytic cell lines. The abnormal cells in PNH have been shown to lack glycosylphosphatidylinositol (GPI)-linked proteins in erythroid, granulocytic, megakaryocytic, and, in some instances, lymphoid cells. Mutations in the phosphatidylinositol glycan A gene, PIGA, have been identified consistently in patients with PNH, thus confirming the biological defect in this disorder. A flow cytometric-based assay can detect the presence or absence of these GPI-linked proteins in granulocytes, monocytes, erythrocytes, and lymphocytes, thus avoiding the problems associated with red cell-based diagnostic methods (Ham test) in which recent hemolytic episodes or recent transfusions can give false-negative results. A partial list of known GPI-linked proteins include CD14, CD16, CD24, CD55, CD56, CD58, CD59, C8-binding protein, alkaline phosphatase, acetylcholine esterase, and a variety of high frequency human blood antigens. In addition, fluorescent aerolysin (FLAER) binds directly to the GPI anchor and can be used to evaluate the expression of the GPI linkage. Our studies, as well as others in the literature, have shown that flow cytometry-based assays will detect all Ham-positive PNH cases, as well as some Ham-negative PNH cases. This assay replaces the sugar water test and the Ham test for the evaluation of patients with possible PNH. Patients with PNH should be transfused with ABO-specific RBCs, which do not need to be washed. If, for some reason, they need to receive non-ABO type-specific (type O) cells, these RBC units should be washed. Since recipient antibodies to granulocyte antigens can trigger hemolytic episodes in PNH, if they have such antibodies these patients should receive leukoreduced RBCs and platelets.

Useful For: Screening for and confirming the diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) Monitoring patients with PNH

Interpretation: Individuals with paroxysmal nocturnal hemoglobinuria (PNH) have absent or decreased expression of all the glycosylphosphatidylinositol (GPI)-linked antigens and fluorescent aerolysin (FLAER) on peripheral blood cells derived from the PNH clone. Recent data showed that small PNH clones can be detected in a relatively high percentage of cases of aplastic anemia and myelodysplastic syndrome. While the significance of this finding is still uncertain, it appears that these patients may benefit from immunosuppressive therapy. This test incorporates a sophisticated technique of separating different cell populations using gating on antigen-positive cells, as well as the sensitivity to enable detection of small PNH clones. In addition, this test detects a partial loss of CD59 on RBCs.
(type II RBC). Patients with large proportion of type II RBC are unlikely to show high levels of hemolysis, unlike patients with complete loss of GPI-linked proteins (predominantly type III cells). While PNH is a disorder of hematopoietic stem cells and all lineages are affected, the percentage of affected cells can differ between lineages, most commonly due to RBC hemolysis and/or transfusion. Individuals without PNH have normal expression of FLAER (neutrophils and monocytes) and normal expression of all GPI-linked antigens-CD14 (monocytes), CD16 (neutrophils and NK cells), CD24 (neutrophils), and CD59 (RBCs).

Reference Values:
An interpretive report will be provided.

RED BLOOD CELLS:
PNH RBC-Partial Antigen loss: 0.00-0.99%
PNH RBC-Complete Antigen loss: 0.00-0.01%
PNH Granulocytes: 0.00-0.01%
PNH Monocytes: 0.00-0.05%


Podoplanin (D2-D40) Immunostain, Technical Component Only

Clinical Information: Podoplanin (D2-40) is a mucin-type transmembrane glycoprotein that is expressed in reactive follicular dendritic cells (FDC), and its expression has been recently reported in FDC sarcomas. Podoplanin is expressed in a variety of other tissues, including lymphatic endothelium, bile duct cells, mesothelial cells, ependyma, myoepithelial cells, and granulosa cells. The D2-40 antibody to podoplanin has been used in the diagnosis of mesothelioma and seminoma.

Useful For: Aids in the identification of reactive follicular dendritic cells

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.
**Clinical References:**

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**FPOLO 75165**

**Polio (Types 1, 3) Antibodies, Neutralization**

**Clinical Information:** This sensitive procedure is recommended for vaccine response testing and type-specific serodiagnosis of recent poliovirus infection. It can also serve as an aid for diagnosing immune deficiency disorders.

**Reference Values:**
- Polio 1 Titer: <1:8
- Polio 3 Titer: <1:8

The presence of neutralizing serum antibodies (titers 1:8 up to >1:128) against polioviruses implies lifelong immunity. Some persons without detectable titers (<1:8) may also be immune as demonstrated by elicitation of a secondary-type serum antibody response upon rechallenge with live polio vaccine.

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**FPOLE 57942**

**Pollock White (Pollachius virens) IgE**

**Interpretation:** Class IgE (kU/L)
- Comment 0 <0.10 Negative
- 0.10 - 0.34 Equivocal/Borderline
- 0.35 - 0.69 Low Positive
- 0.70 - 3.49 Moderate Positive
- 3.50 - 17.49 High Positive
- 17.50 - 49.99 Very High Positive
- 50.00 - 99.99 Very High Positive
- >99.99 Very High Positive

**Reference Values:**
- <0.35 kU/L

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**PVJAK 65116**

**Polycythemia Vera, JAK2 V617F with Reflex to JAK2 Exon 12-15, Sequencing for Erythrocytosis**

**Clinical Information:** The Janus kinase 2 gene (JAK2) codes for a tyrosine kinase (JAK2) that is associated with the cytoplasmic portion of a variety of transmembrane cytokine and growth factor receptors important for signal transduction in hematopoietic cells. Signaling via JAK2 activation causes phosphorylation of downstream signal transducers and activators of transcription (STAT) proteins (eg, STAT5) ultimately leading to cell growth and differentiation. The JAK2 V617F is located in exon 14 and present in 50% to 60% of primary myelofibrosis and essential thrombocythemia, and 95% to 98% of polycythemia vera (PV). In the rest of the polycythemia vera cases, over 50 different mutations have been reported within exons 12 through 15 of JAK2 and essentially all of the non-V617F JAK2 mutations have been identified in polycythemia vera. These mutations include point mutations and small insertions or deletions. Several of the exon 12 mutations have been shown to have biologic effects similar to those caused by the V617F mutation such that it is currently assumed other nonpolymorphic mutations have similar clinical effects. However, some mutations may not be well characterized and requires further clinical and research evaluation.

**Useful For:** Aiding in the distinction between the myeloproliferative neoplasm polycythemia vera (PV) and other secondary erythrocytosis

**Interpretation:** The results will be reported as 1 of the 3 following states:
- Positive for JAK2 V617F mutation
- Positive for JAK2 mutation (other than V617F)
- Negative for JAK2 mutations
If the result is positive, a description of the mutation at the nucleotide level and the altered protein sequence are reported. A positive mutation status is highly suggestive of a myeloid neoplasm and may support a
diagnosis of polycythemia vera in the appropriate clinical setting. Correlation with clinicopathologic findings and other laboratory results is necessary in all cases. A negative mutation status makes a diagnosis of polycythemia vera highly unlikely, although it does not completely exclude this possibility, other myeloproliferative neoplasms or other neoplasms.

**Reference Values:**
An interpretive report will be provided


**TALDO 61843**

**Polyols, Quantitative, Urine**

**Clinical Information:** Polyols are sugar alcohols that have been identified in blood, urine, and cerebrospinal fluid. Characteristic patterns of abnormal polyols may suggest a disorder of the pentose phosphate pathway (PPP) including transaldolase (TALDO) deficiency and ribose-5-phosphate isomerase (RPI) deficiency. The PPP is involved in carbohydrate metabolism and is present in the cytosol of all cells. Two specific functions of the PPP are the production of nicotinamide adenine dinucleotide phosphate (NADPH) and the synthesis of ribose-5-phosphate, a molecule necessary for nucleotide and nucleic acid synthesis. Both TALDO and RPI deficiency that have multisystem involvement are recently described disorders of this pathway. TALDO deficiency is an autosomal recessive disorder caused by a reduction of the enzyme transaldolase. Clinical manifestations are characterized by severe neonatal liver failure, coagulopathy, low serum protein, hypoglycemia, high ammonia, progressive myocardial hypertrophy, and abnormal lactate dehydrogenase with remarkably normal or low transaminases. Patients may present in the antenatal period with maternal HELLP syndrome (hemolysis, elevated liver enzymes, low platelets), hydrops fetalis and oligohydramnios, dysmorphic features, cutis laxa, and hypertrichosis. The clinical course is variable, but acute liver failure with normal transaminases is a common finding.

Initially, hepatomegaly is absent, but the spleen may be enlarged. Later, hepatomegaly with liver cirrhosis and mild kidney failure occur. RPI deficiency is an autosomal recessive disorder caused by a deficiency of the enzyme ribose-5-phosphate isomerase. Clinical manifestations include neurological deficits such as slow progressing leukoencephalopathy and neuropathy. Additionally, spasticity, ataxia, epilepsy, regression, and delayed psychomotor development have been described. Polyol analysis in urine is the method of choice for the biochemical diagnosis of TALDO and RPI deficiency. Abnormal results should be followed with either enzymatic or molecular genetic analysis.

**Useful For:** Diagnosis of transaldolase (TALDO) deficiency or ribose-5-phosphate isomerase (RPI) deficiency

**Interpretation:** An interpretive report is provided. All profiles are reviewed by the laboratory director and interpretation is based on pattern recognition. A detailed interpretation is given, including an overview of the results and of their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing and in vitro confirmatory studies (enzyme assay, molecular analysis), name and phone number of key contacts who may provide these studies at Mayo or elsewhere, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Polyols (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-11 months</td>
<td>0-11 months</td>
</tr>
<tr>
<td>1-3 years</td>
<td>1-3 years</td>
</tr>
<tr>
<td>4-17 years</td>
<td>4-17 years</td>
</tr>
<tr>
<td>&gt; or =18 years</td>
<td>&gt; or =18 years</td>
</tr>
</tbody>
</table>
**Clinical References:**

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**Pomegranate (Punica granatum) IgE**

**Interpretation:**
- Class IgE (kU/L)
- Comment 0 < 0.35 Below Detection
- 1 0.35 – 0.69 Low Positive
- 2 0.70 – 3.49 Moderate Positive
- 3 3.50 – 17.49 Positive
- 4 17.50 – 49.99 Strong Positive
- 5 50.00 – 99.99 Very Strong Positive
- 6 > 99.99 Very Strong Positive

**Reference Values:**
- < 0.35 kU/L

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**Pompe Disease Second-Tier Newborn Screening, Blood Spot**

**Clinical Information:** Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA; acid maltase) due to mutations in the GAA gene. The estimated incidence is 1 in 40,000 live births. In Pompe disease, glycogen that is taken up by lysosomes during physiologic cell turnover accumulates, causing lysosomal swelling, cell damage and, eventually, organ dysfunction. This leads to progressive muscle weakness, cardiomyopathy, and, eventually, death. Patients with Pompe disease, especially those with infantile, childhood, and juvenile onset, can have elevations of serum enzymes (such as creatine kinase) secondary to cellular dysfunction. The clinical phenotype of Pompe disease lies on a spectrum, with differing clinical phenotypes dependent on age of onset and residual enzyme activity. Complete loss of enzyme activity causes onset in infancy leading to death, typically within the first year of life when left untreated. Juvenile and adult-onset forms, as the names suggest, are characterized by later onset and longer survival. All disease variants are eventually associated with progressive muscle weakness and respiratory insufficiency. Cardiomyopathy is associated almost exclusively with the infantile form. Treatment with enzyme replacement therapy is available, making early diagnosis of Pompe disease desirable, as early initiation of treatment may improve prognosis. Newborn screening can identify patients with all forms of Pompe disease, even before onset of symptoms. Unaffected patients with GAA pseudodeficiency alleles and carriers may also be identified by newborn screening. The ratio calculated between the creatine (Cre):creatinine (Crn) ratio as the numerator and the activity of GAA as the denominator can differentiate true cases of infantile and late-onset Pompe disease from false-positive cases (such as carriers and pseudodeficiency of GAA enzyme). When applied to the newborn screening setting, this second-tier testing can provide results in a timely fashion and provide better guidance in the decision to submit samples for further confirmatory testing by molecular genetic analysis (GAAZ / Pompe Disease, Full Gene Analysis).

**Useful For:** Second-tier testing of newborns with an abnormal primary screening result/decreased GAA enzyme for Pompe disease Follow-up testing for evaluation of an abnormal newborn screening
result for Pompe disease

**Interpretation:** An interpretive report is provided. The quantitative measurements of informative metabolites and related ratios are evaluated using the Collaborative Laboratory Integrated Reports (CLIR) system. The report is in text form only, indicating if the applicable ratio is normal or abnormal and whether or not the CLIR postanalytical tool is informative for Pompe disease. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis, independent biochemical (ie, in vitro enzyme assay) or molecular genetic analyses are required, many of which are offered within Mayo Clinic's Division of Laboratory Genetics and Genomics. Recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis) are provided in the interpretative report.

**Reference Values:**
An interpretive report is provided.

**Clinical References:**

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**Pompe Disease, Full Gene Analysis**

**Clinical Information:** Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive condition caused by deficiency of acid alpha-glucosidase. Enzyme insufficiency results in symptoms such as muscle weakness, cardiomyopathy, and respiratory problems. Mutations in the GAA gene (which encodes acid alpha-glucosidase) are associated with Pompe disease. The diagnosis of this heterogeneous condition relies on both clinical and laboratory evaluation. Clinically, the condition is categorized into infantile and late-onset forms based on age of onset, organ involvement, and rate of progression. The infantile form (or classic Pompe disease) is the most severe form and is characterized by early onset and rapid progression of cardiac, liver, and muscle problems resulting in death within the first year. The infantile variant form has a similar age of onset but a milder clinical presentation. On the less severe end of the spectrum is the late-onset form with childhood, juvenile, or adult onset. The rate of progression and severity of symptoms is quite variable, particularly in the late-onset forms. The incidence varies by clinical type and ethnic population; the combined incidence is approximately 1 in 40,000 individuals. Biochemical testing of acid alpha-glucosidase in blood spot specimens or fibroblasts is useful for individuals with a suspected diagnosis of Pompe disease (GAABS / Acid Alpha-Glucosidase, Blood Spot). When clinical manifestations and results of that analysis are supportive of a diagnosis of Pompe disease, mutation analysis of the GAA gene is warranted. Over 250 different mutations have been identified in this gene including point mutations and large deletions. GAA full gene sequencing provided by this test will detect 2 mutations in approximately 83% to 93% of individuals with confirmed GAA enzyme deficiency. Identification of mutations provides confirmation of the diagnosis and allows for subsequent testing of at risk family members.

**Useful For:** Confirmation of diagnosis of Pompe disease (as a follow-up to biochemical analyses)

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Poplar White (Populus alba) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

Poppy Seed, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.

**Clinical References:** Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and Management by Laboratory Methods. 21st edition. Edited by RA McPherson, MR Pincus. WB
**Pork IgG**

**Interpretation:** mcg/mL of IgG  
Lower Limit of Quantitation 2.0  
Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Pork IgG4**

**Interpretation:** mcg/mL of IgG4  
Lower Limit of Quantitation 0.15  
Upper Limit of Quantitation 30.0

**Reference Values:**

<0.15 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicated immunologic sensitization to the food allergen in question.

**Pork Neutral-Regular Insulin, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
### Clinical References


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### Pork, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69 Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49 Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4 Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9 Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9 Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100 Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

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**PBALP 64661**

**Porphobilinogen and Aminolevulinic Acid, Plasma**

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma, and the excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, of the 5 hepatic porphyrias, 4 typically present with acute neurological manifestations and are designated the acute porphyrias. Clinically, however, these attacks can be prolonged and chronic. Three primary acute hepatic porphyrias: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms which typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. A broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes may precipitate crises. Photosensitivity is not associated with AIP, but may be present in HCP and VP. Plasma porphobilinogen (PBG) and aminolevulinic acid (ALA) are elevated during the acute phase of these neurologic porphyrias. Urine and fecal porphyrin analysis should be performed to confirm the diagnosis and to distinguish among AIP, HCP, and VP. A biochemical diagnosis of AIP can be confirmed by measurement of PBG deaminase activity (PBGD, / Porphobilinogen Deaminase [PBGD], Whole Blood). VP and HCP can be confirmed by measurement of fecal porphyrins (FQPPS / Porphyrins, Feces). Once the biochemical diagnosis of an acute porphyria is established, molecular genetic testing is available for AIP (HMBSZ / HMBS Gene, Full Gene Analysis), HCP (CPOXZ / CPOX Gene, Full Gene Analysis), or VP (PPOXZ / PPOX Gene, Full Gene Analysis) which allows for diagnosis of at-risk family members. The very rare (∼10 cases described) autosomal recessive aminolevulinic acid dehydratase deficiency porphyria (ADP) is also a primary acute porphyria causing neurovisceral symptoms. It presents in childhood and biochemically, it is characterized by an isolated significant elevation of aminolevulinic acid (ALA). More commonly, however, isolated elevations of ALA are due to secondary inhibition of ALA dehydratase. Among the secondary causes, acute lead intoxication results in the highest degree of aminolevulinic aciduria. Less significant elevations are seen in chronic lead intoxication and tyrosinemia type I. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies.

**Useful For:** An equivalent option to urine for first-line test for evaluation of a suspected acute porphyria Monitoring patients undergoing treatment for an acute intermittent porphyria or other acute porphyria

**Interpretation:** Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

- Porphobilinogen: < or =0.5 nmol/mL
- Aminolevulinic Acid: < or =0.5 nmol/mL


Porphobilinogen Deaminase (PBGD), Washed Erythrocytes

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Acute intermittent porphyria (AIP) is caused by diminished erythrocyte activity of porphobilinogen deaminase (PBGD), also known as uroporphyrinogen I synthase or hydroxymethylbilane synthase. Onset of AIP typically occurs during puberty or later. Individuals may experience acute episodes of neuropathic symptoms. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. Crises may be precipitated by a broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes. AIP is inherited in an autosomal dominant manner. At-risk family members of patients with a biochemical diagnosis of AIP should undergo appropriate testing. Timely diagnosis is important as acute episodes of AIP can be fatal. Treatment of AIP includes the prevention of symptoms through avoidance of precipitating factors. More than 80% of individuals with deficiency mutation in the HMBS gene remain asymptomatic throughout their lives. The biochemical diagnosis of AIP is made by demonstrating increased urinary excretion of porphobilinogen (PBG) and is most accurate during an acute episode. In addition, the diagnosis of AIP can be confirmed through the measurement of porphobilinogen deaminase (PBGD) enzyme activity in erythrocytes, although 5% to 10% of affected individuals exhibit normal erythrocyte PBGD activity. In addition, molecular genetic confirmation (HMBSZ / HMBS Gene, Full Gene Analysis) is available on a clinical basis and can be particularly helpful in identifying asymptomatic family members at risk of acute symptoms. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies.

Useful For: Confirmation of a diagnosis of acute intermittent porphyria

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach a laboratory director in case the referring physician has additional questions.

Reference Values:
Reference ranges have not been established for patients who are <16 years of age.

> or =7.0 nmol/L/sec
6.0-6.9 nmol/L/sec (indeterminate)
<6.0 nmol/L/sec (diminished)


Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
**Porphobilinogen Deaminase (PBGD), Whole Blood**

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Acute intermittent porphyria (AIP) is caused by diminished erythrocyte activity of porphobilinogen deaminase (PBGD), also known as uroporphyrinogen I synthase or hydroxymethylbilane synthase. Onset of AIP typically occurs during puberty or later. Individuals may experience acute episodes of neuropathic symptoms. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. Crises may be precipitated by a broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes. AIP is inherited in an autosomal dominant manner. At-risk family members of patients with a biochemical diagnosis of AIP should undergo appropriate testing. Timely diagnosis is important as acute episodes of AIP can be fatal. Treatment of AIP includes the prevention of symptoms through avoidance of precipitating factors. More than 80% of individuals with deficiency mutation in the HMBS gene remain asymptomatic throughout their lives. The biochemical diagnosis of AIP is made by demonstrating increased urinary excretion of porphobilinogen (PBG) and is most accurate during an acute episode. In addition, the diagnosis of AIP can be confirmed through the measurement of porphobilinogen deaminase (PBGD) enzyme activity in erythrocytes, although 5% to 10% of affected individuals exhibit normal erythrocyte PBGD activity. In addition, molecular genetic confirmation (HMBSZ / HMBS Gene, Full Gene Analysis) is available on a clinical basis and can be particularly helpful in identifying asymptomatic family members at risk of acute symptoms. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies.

**Useful For:** Confirmation of a diagnosis of acute intermittent porphyria (AIP)

**Interpretation:** Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach a laboratory director in case the referring physician has additional questions.

**Reference Values:**
Reference ranges have not been established for patients who are <16 years of age.

- \( > 7.0 \text{ nmol/L/sec} \)
- 6.0-6.9 nmol/L/sec (indeterminate)
- <6.0 nmol/L/sec (diminished)

**Clinical References:**

**Porphobilinogen, Quantitative, Random, Urine**

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrias can be further classified...
as chronic or acute, based on their clinical presentation. The primary acute hepatic porphyrias: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms that typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. A broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes may precipitate crises. Photosensitivity is not associated with AIP, but may be present in HCP and VP. Urinary porphobilinogen (PBG) is elevated during the acute phase of the neurologic porphyrias. Urine and fecal porphyrin analysis should be performed to confirm the diagnosis and to distinguish between AIP, HCP, and VP. A biochemical diagnosis of AIP can be confirmed by measurement of PBG deaminase activity using PBGD / Porphobilinogen Deaminase (PBGD). VP and HCP can be confirmed by measurement of fecal porphyrins (FQPPS / Porphyrins, Feces).

Once the biochemical diagnosis of an acute porphyria is established, molecular genetic testing is available, which allows for diagnosis of at-risk family members. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies.

**Useful For:** First-order test for evaluation of a suspected acute porphyria: acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria

**Interpretation:** Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**
< or =1.3 mc mole/L

**Clinical References:**

**Porphyris Evaluation, Washed Erythrocytes**

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. Testing erythrocyte porphyrin level is most informative for patients with a clinical suspicion of erythropoietic protoporphyrinia (EPP) or X-linked dominant protoporphyrinia (XLDP). Clinical presentation of EPP and XLDP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Although genetic in nature, environmental factors exacerbate symptoms, significantly impacting the severity and course of disease. EPP is caused by decreased ferrochelatase activity resulting in significantly increased free protoporphyrin levels in erythrocytes, plasma, and feces. X-linked dominant protoporphyrinia is caused by gain-of-function mutations in the C-terminal end of ALAS2 gene and results in elevated erythrocyte levels of free and zinc-complexed protoporphyrin, and total protoporphyrin levels in plasma and feces. Protoporphyrin fraction is the main component of erythrocyte porphyrins. When total erythrocyte porphyrins are elevated, fractionation and quantitation

Porphyrias Evaluation, Whole Blood Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. Testing erythrocyte porphyrin level is most informative for patients with a clinical suspicion of erythropoietic protoporphyria (EPP) or X-linked dominant protoporphyrinia (XLDPP). Clinical presentation of EPP and XLDPP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Although genetic in nature,
environmental factors exacerbate symptoms, significantly impacting the severity and course of disease.

EPP is caused by decreased ferrochelatase activity resulting in significantly increased free protoporphyrin levels in erythrocytes, plasma, and feces. X-linked dominant protoporphyria is caused by gain-of-function mutations in the C-terminal end of ALAS2 gene and results in elevated erythrocyte levels of free and zinc-complexed protoporphyrin, and total protoporphyrin levels in plasma and feces. Protoporphyrin fraction is the main component of erythrocyte porphyrins. When total erythrocyte porphyrins are elevated, fractionation and quantitation of zinc-complexed and noncomplexed (free) protoporphyrin is necessary to differentiate the inherited porphyrias from other causes of elevated porphyrin levels. Other possible causes of elevated erythrocyte zinc-complexed protoporphyrin may include: -Iron-deficiency anemia, the most common cause -Chronic intoxication by heavy metals (primarily lead) or various organic chemicals -Congenital erythropoietic porphyria (CEP), a rare autosomal recessive porphyria caused by deficient uroporphyrinogen III synthase -Hepatoerythropoietic porphyria, a rare autosomal recessive porphyria caused by deficient uroporphyrinogen decarboxylase Typically, the workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies. There are 2 test options: PEE / Porphyrins Evaluation, Whole Blood and PEWE / Porphyrins Evaluation, Washed Erythrocytes. The whole blood option is easiest for clients but requires that the specimen arrive at Mayo Medical Laboratories within 7 days of draw. When this cannot be ensured, washed frozen erythrocytes, which are stable for 14 days, should be submitted.

Useful For: Establishing a biochemical diagnosis of erythropoietic protoporphyria and X-linked dominant protoporphyria

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.

Reference Values:

PORPHYRINS, TOTAL, RBC
<80 mcg/dL packed cells

FREE PROTOPORPHYRIN
<20 mcg/dL packed cells

ZINC-COMPLEXED PROTOPORPHYRIN
<60 mcg/dL packed cells

Clinical References:

Porphyris, Feces

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin
accumulation in erythrocytes and plasma, and excretion of the heme precursors in urine and feces allow
for the detection and differentiation of the porphyrias. The porphyrias are typically classified as
erthrotypoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic
porphyrias can be further classified as chronic or acute, based on their clinical presentation. The primary
acute hepatic porphyrias: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and
variegate porphyria (VP), are associated with neurovisceral symptoms, which typically onset during
puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and
psychiatric symptoms. Crises may be precipitated by a broad range of medications (including
barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes.
Photosensitivity is not associated with AIP, but may be present in HCP and VP. Cutaneous
photosensitivity is associated with the chronic hepatic porphyrias: porphyria cutanea tarda (PCT) and
the erythropoietic porphyrias; erythropoietic protoporphyria (EPP), X-linked dominant protoporphyria
(XLDPP), and congenital erythropoietic porphyria (CEP). Although genetic in nature, environmental
factors may exacerbate symptoms, significantly impacting the severity and course of disease. CEP is an
erthropoietic porphyria caused by uroporphyrinogen III synthase deficiency. Symptoms typically
present in early infancy with red-brown staining of diapers, severe cutaneous photosensitivity with
fluid-filled bullae and vesicles. Other common symptoms may include thickening of the skin, hypo- and
hyperpigmentation, hypertrichosis, cutaneous scarring, and deformities of the fingers, eyelids, lips,
nose, and ears. A few milder adult-onset cases have been documented as well as cases that are
secondary to myeloid malignancies. PCT is the most common form of porphyria and is most commonly
sporadic (acquired), but in about 25% of cases it is inherited in an autosomal dominant manner. The
most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed
surfaces. Patients experience chronic blisters, lesions resulting from mild trauma to sun-exposed areas.
These fluid-filled vesicles rupture easily, become crusted, and heal slowly. Secondary infections can
cause areas of hypo- or hyperpigmentation or sclerodermatous changes and may result in the
development of alopecia at sites of repeated skin damage. Liver disease is common in patients with PCT
as evidenced by abnormal liver function tests and 30% to 40% of patients developing cirrhosis. In
addition, there is an increased risk of hepatocellular carcinoma. Hepatoerythropoietic porphyria (HEP)
occurs when an individual inherits PCT from both parents. Patients exhibit a similar clinical
presentation to what is seen in CEP. Clinical presentation of EPP and XLDPP is identical with onset of
symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin
generally worsens in the spring and summer months. Common symptoms may include itching, edema,
erthema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas.
Increased fecal porphyrin excretions are observed most commonly in symptomatic patients with CEP,
PCT, HCP, and VP. In quiescent phases, as well as prior to puberty, fecal porphyrin excretion may be
within normal limits. Patients with AIP may have elevated fecal porphyrin levels during severe attacks.
EPP and XLDPP patients may have elevated protoporphyrin levels, however, these disorders cannot be
diagnosed by fecal analysis alone. The workup of patients with a suspected porphyria is most effective
when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria
(Cutaneous) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies.

Useful For:
Evaluation of patients who present with signs or symptoms suggestive of porphyria
cutanea tarda, hereditary coproporphyria, variegate porphyria, congenital erythropoietic porphyria,
erthropoietic protoporphyria, or X-linked dominant protoporphyria

Interpretation:
Abnormal results are reported with a detailed interpretation that may include an
overview of the results and their significance, a correlation to available clinical information provided with
the specimen, differential diagnosis, recommendations for additional testing when indicated and available,
and a phone number to reach one of the laboratory directors in case the referring physician has additional
questions.

Reference Values:
UROPOPHORYRIN I
<120 mcg/24 hours

UROPOPHORYRIN III
<50 mcg/24 hours

HEPTACARBOXYL PORPHYRIN I
HEPTACARBOXYL PORPHYRIN III
<40 mcg/24 hours

ISOHEPTACARBOXYL PORPHYRINS
<30 mcg/24 hours

HEXACARBOXYL PORPHYRIN I
<10 mcg/24 hours

HEXACARBOXYL PORPHYRIN III
<10 mcg/24 hours

ISOHEXACARBOXYL PORPHYRINS
<10 mcg/24 hours

PENTACARBOXYL PORPHYRIN I
<20 mcg/24 hours

PENTACARBOXYL PORPHYRIN III
<20 mcg/24 hours

ISOPENTACARBOXYL PORPHYRINS
<80 mcg/24 hours

COPROPORPHYRIN I
<500 mcg/24 hours

COPROPORPHYRIN III
<400 mcg/24 hours

ISOCOPROPORPHYRIN
<200 mcg/24 hours

PROTOPORPHYRINS
<1,500 mcg/24 hours

COPROPORPHYRIN III/COPROPORPHYRIN I RATIO
<1.20

See The Heme Biosynthetic Pathway in Special Instructions.

**Clinical References:**
porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrias can be further classified as chronic or acute, based on their clinical presentation. The primary acute hepatic porphyrias: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are associated with neurovisceral symptoms that typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. Crises may be precipitated by a broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes. Photosensitivity is not associated with AIP, but may be present in HCP and VP. Cutaneous photosensitivity is associated with the chronic hepatic porphyrias: porphyria cutanea tarda (PCT) and the erythropoietic porphyrias; erythropoietic protoporphyrinia (EPP), X-linked dominant protoporphyrinia (XLDPP), and congenital erythropoietic porphyria (CEP). Although genetic in nature, environmental factors may exacerbate symptoms, significantly impacting the severity and course of disease. CEP is an erythropoietic porphyria caused by uroporphyrinogen III synthase deficiency. Symptoms typically present in early infancy with red-brown staining of diapers, severe cutaneous photosensitivity with fluid-filled bullae and vesicles. Other common symptoms may include thickening of the skin, hyperpigmentation, hypertrichosis, cutaneous scarring, and deformities of the fingers, eyelids, lips, nose, and ears. A few milder adult-onset cases have been documented as well as cases that are secondary to myeloid malignancies. PCT is the most common form of porphyria and is most commonly sporadic (acquired) but in about 25% of cases it is inherited in an autosomal dominant manner. The most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions resulting from mild trauma to sun-exposed areas. These fluid-filled vesicles rupture easily, become crusted, and heal slowly. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and may result in the development of alopecia at sites of repeated skin damage. Liver disease is common in patients with PCT as evidenced by abnormal liver function tests and with 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma. Hepatoerythropoietic porphyria (HEP) is observed when an individual inherits PCT from both parents. Patients exhibit a similar clinical presentation to what is seen in CEP. Urinary porphyrin determination is helpful in the diagnosis of most porphyrias including CEP, PCT, AIP, HCP, and VP. In addition, measurement of porphobilinogen (PBG) in urine is important in establishing the diagnosis of the acute neurologic porphyrias (AIP, HCP and VP). Neither urine porphyrins nor PBG is helpful in evaluating patients suspected of having EPP or XLDPP. In addition, porphyrinuria may result from exposure to certain drugs and toxins or other medical conditions (ie, hereditary tyrosinemia type I). Heavy metals, halogenated solvents, various drugs, insecticides, and herbicides can interfere with heme production and cause "intoxication porphyria." Chemically, the intoxication porphyrias are characterized by increased excretion of uroporphyrin and/or coproporphyrin in urine. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies.

**Useful For:** Preferred screening test for congenital erythropoietic porphyria and porphyria cutanea tarda and during symptomatic periods for acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria when specimen transport will be longer than 72 hours

**Interpretation:** Abnormal results are reported with a detailed interpretation which may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

**UROPORPHYRINS (OCTACARBOXYL)**

< or =30 nmol/24 hours

**HEPTACARBOXYLPORPHYRINS**

< or =9 nmol/24 hours
HEXACARBOXYLPORPHYRINS
< or =8 nmol/24 hours

PENTACARBOXYLPORPHYRINS
< or =10 nmol/24 hours

COPROPORPHYRINS (TETRACARBOXYL)
Males: < or =230 nmol/24 hours
Females: < or =168 nmol/24 hours

PORPHOBILINOGEN
< or =2.2 mcmol/24 hours

Clinical References:

Porphyrins, Quantitative, Random, Urine

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrinas can be further classified as chronic or acute, based on their clinical presentation. The primary acute hepatic porphyrinas: acute intermittent porphyrin (AIP), hereditary coproporphyria (HCP), and variegate porphyrin (VP), are associated with neurovisceral symptoms that typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. Crises may be precipitated by a broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes. Photosensitivity is not associated with AIP, but may be present in HCP and VP. Cutaneous photosensitivity is associated with the chronic hepatic porphyrias: porphyria cutanea tarda (PCT) and the erythropoietic porphyrias; erythropoietic protoporphyria (EPP), X-linked dominant protoporphyria (XLDPP), and congenital erythropoietic porphyria (CEP). Although genetic in nature, environmental factors may exacerbate symptoms, significantly impacting the severity and course of disease. CEP is an erythropoietic porphyrin caused by uroporphyrinogen III synthase deficiency. Symptoms typically present in early infancy with red-brown staining of diapers, severe cutaneous photosensitivity with fluid-filled bullae and vesicles. Other common symptoms may include thickening of the skin, hypo- and hyperpigmentation, hypertrichosis, cutaneous scarring, and deformities of the fingers, eyelids, lips, nose, and ears. A few milder adult-onset cases have been documented as well as cases that are secondary to myeloid malignancies. PCT is the most common form of porphyria and is most commonly sporadic (acquired) but in about 25% of cases it is inherited in an autosomal dominant manner. The most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions resulting from mild trauma to sun-exposed areas. These fluid-filled vesicles rupture easily, become crusted, and heal slowly. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and may result in the development of alopecia at sites of repeated skin damage. Liver disease is common in patients with PCT as evidenced by abnormal liver function tests and with 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma. Hepatoerythropoietic porphyrin (HEP) is observed when an individual inherits PCT from both parents. Patients exhibit a similar clinical
presentation to what is seen in CEP. In addition, porphyrinuria may result from exposure to certain drugs and toxins or other medical conditions (ie, hereditary tyrosinemia type I). Heavy metals, halogenated solvents, various drugs, insecticides, and herbicides can interfere with heme production and cause "intoxication porphyria." Chemically, the intoxication porphyrias are characterized by increased excretion of, uroporphyrin and/or coproporphyrin in urine. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies.

**Useful For:** Preferred test to begin assessment for congenital erythropoietic porphyria and porphyria cutanea tarda and during symptomatic periods for acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria when specimen transport will not exceed 72 hours

**Interpretation:** Abnormal results are reported with a detailed interpretation which may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach 1 of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**
- **UROPORPHYRINS, OCTA**
  - < or =30 nmol/L

- **HEPTACARBOXYLPORPHYRINS**
  - < or =7 nmol/L

- **HEXACARBOXYLPORPHYRINS**
  - < or =2 nmol/L

- **PENTACARBOXYLPORPHYRINS**
  - < or =5 nmol/L

- **COPROPORPHYRINS, TETRA**
  - < or =110 nmol/L

- **PORPHOBILINOGEN**
  - < or =1.3 mcmol/L


**PTP**

**Porphyrians, Total, Plasma**

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. The porphyrias are typically classified as erythropoietic or hepatic based upon the primary site of the enzyme defect. In addition, hepatic porphyrias can be further classified as chronic or acute, based on their clinical presentation. The primary acute hepatic porphyrias, acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), are...
associated with neurovisceral symptoms that typically onset during puberty or later. Common symptoms include severe abdominal pain, peripheral neuropathy, and psychiatric symptoms. A broad range of medications (including barbiturates and sulfa drugs), alcohol, infection, starvation, heavy metals, and hormonal changes may precipitate crises. Photosensitivity is not associated with AIP, but may be present in HCP and VP. Cutaneous photosensitivity is associated with the chronic hepatic porphyria, porphyria cutanea tarda (PCT), and the erythropoietic porphyrrias including erythropoietic protoporphyria (EPP), X-linked dominant protoporphyria (XLDPP), and congenital erythropoietic porphyria (CEP). Although genetic in nature, environmental factors may exacerbate symptoms, significantly impacting the severity and course of disease. CEP is an erythropoietic porphyria caused by uroporphyrinogen III synthase deficiency. Symptoms typically present in early infancy with red-brown staining of diapers, severe cutaneous photosensitivity with fluid-filled bullae and vesicles. Other common symptoms may include thickening of the skin, hypo- and hyperpigmentation, hypertrichosis, cutaneous scarring, and deformities of the fingers, eyelids, lips, nose, and ears. A few milder adult-onset cases have been documented as well as cases that are secondary to myeloid malignancies. PCT is the most common form of porphyria and can be either sporadic (acquired) or inherited in an autosomal dominant manner. The most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions resulting from mild trauma to sun-exposed areas. These fluid-filled vesicles rupture easily, become crusted, and heal slowly. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and alopecia may develop at sites of repeated skin damage. Liver disease is common in patients with PCT as evidenced by abnormal liver function tests with 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma. Hepatoerythropoietic porphyria (HEP) occurs when an individual inherits PCT from both parents. Patients exhibit a similar clinical presentation to what is seen in CEP. Clinical presentation of EPP and XLDPP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Plasma porphyrins are most appropriate for monitoring treatment of PCT. Although analysis in plasma is not recommended for diagnosis, increases in plasma porphyrin concentrations are observed in the cutaneous porphyrias and may be elevated during acute episodes of AIP, VP, and HCP. In addition, persons in chronic renal failure who develop bullous dermatosis similar to that associated with PCT may have increased plasma porphyrins. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies.

Useful For: Monitoring treatment of patients with porphyria cutanea tarda

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
< or =1.0 mcg/dL


POSA
89591

Posaconazole, Serum

Clinical Information: Posaconazole interferes with fungal cytochrome P450 (CYP) (lanosterol-14 alpha demethylase) activity, decreasing synthesis of ergosterol, the principal sterol in fungal cell
membrane, and inhibiting fungal cell membrane formation.(1,3) Posaconazole has been approved for prophylaxis of invasive Aspergillus and Candida infections in severely immunocompromised patients (eg, hematopoietic stem cell transplant recipients with graft-versus-host disease: GVHD or those with prolonged neutropenia secondary to chemotherapy for hematologic malignancies) and treatment of oropharyngeal candidiasis (including patients refractory to itraconazole and/or fluconazole).(1,2) It also is approved for ocular administration (drug monitoring not required for this use). Posaconazole has a variable absorption. Food and liquid nutritional supplements increase absorption and fasting states do not provide sufficient absorption to ensure adequate plasma concentrations.(4,5) The drug has a high volume of distribution (Vd=465-1,774 L) and is highly protein bound (> or =97%), predominantly bound to albumin.(1,2) The drug does not undergo significant metabolism; approximately 15% to 17% undergoes non-CYP-mediated metabolism, primarily via hepatic glucuronidation into metabolites.(1) The half-life elimination is approximately 35 hours (range: 20-66 hours); steady-state is achieved after about 5 to 7 days. Time to maximum concentration is approximately 3 to 5 hours but, due to the highly variable absorption, trough level monitoring is recommended. Therapeutic drug monitoring should be considered in the following situations: -To document optimal absorption when used for prophylaxis or active treatment of a fungal infection -Consider rechecking a level even if initial level was in the goal range if the patient: - Is unable to meet optimal nutritional intake - Is receiving continuous tube feeding - Is receiving a proton pump inhibitor (decreased posaconazole levels in some studies) - Has mucositis, diarrhea, vomiting, GVHD, or other reason that he/she may not absorb the drug well

Useful For: Monitoring of posaconazole therapy

Interpretation: Greater than 700 ng/mL (>0.7 mcg/mL) has been suggested for prophylaxis and also in a salvage trial for treatment of invasive Aspergillus infections.

Reference Values:
>700 ng/mL (trough)


POSV 9205

Post Vasectomy Check, Semen

Clinical Information: Following a vasectomy, sperm may be found in the semen for 6 weeks to 3 months or longer. Regular ejaculation (every 3-4 days) may eliminate sperm from the reproductive tract more quickly. To check for the absence of sperm, semen should be evaluated for the presence of sperm 3 months postvasectomy and after a minimum of 20 ejaculations. Because the sperm count may be very low, the semen is centrifuged for concentration purposes. A negative result from 1 well-mixed postvasectomy semen specimen generally indicates that use of contraception is no longer necessary. Occasional cases have been reported where postvasectomy semen analysis (PVSA) shows intermittent presence of rare nonmotile sperm (RNMS) in the semen.(1)

Useful For: Determining absence or presence of sperm postvasectomy

Interpretation: Patients may stop using other methods of contraception when examination of 1 well-mixed postvasectomy semen specimen shows azoospermia or rare nonmotile sperm (RNMS < or = 100,000 nonmotile sperm/mL). The risk of pregnancy after vasectomy is approximately 1 in 2,000 for men who have postvasectomy azoospermia or postvasectomy semen analysis (PVSA) showing RNMS.(1) If >100,000 nonmotile sperm/mL persist beyond 6 months after vasectomy, then trends of serial PVSAs and clinical judgment should be used to decide whether the vasectomy is a failure and whether repeat vasectomy should be considered.(1) Vasectomy should be considered a failure if any motile sperm are seen on PVSA at 6 months after vasectomy, in which case repeat vasectomy should be considered.
PMARP
65559

Postmortem Arrhythmia Panel

Clinical Information: Sudden cardiac death (SCD) is estimated to occur at an incidence of between 50 to 100 per 100,000 individuals in North America and Europe each year, claiming between 250,000 and 450,000 lives in the United States annually. In younger individuals (ages 15-35), the incidence of SCD is between 1 to 2 per 100,000 young individuals. The reported incidence of SCD is likely an underestimate since more overt causes of death, such as car accidents and drownings, may result from arrhythmogenic events. In cases of sudden unexplained death where autopsy does not detect a structural basis for sudden death, a hereditary arrhythmia may be suspected. Brugada syndrome (BrS) and long QT syndrome (LQTS) are inherited forms of cardiac arrhythmia that may cause sudden cardiac death. Postmortem diagnosis of a hereditary arrhythmia may assist in confirmation of the cause and manner of death, as well as risk assessment in living family members. BrS is a genetic cardiac disorder characterized by ST segment elevation in leads V1-V3 on electrocardiography (EKG) with a high risk for ventricular arrhythmias that can lead to sudden cardiac death. BrS is inherited in an autosomal dominant manner and is caused by pathogenic variants in genes that encode cardiac ion channels. The diagnosis of BrS is established based on the characteristic EKG abnormality along with personal and family health history, and also requires exclusion of other causes including cardiac structural abnormalities, medications, and electrolyte imbalances. Genes associated with BrS include CACNA1C, CACNA2D1, GPD1L, KCNE3, KCNJ8, SCN3B, CACNB2, SCN1B, and SCN5A. Additional clinical information about BrS can be found in MML’s BRGGP / Brugada Syndrome Multi-Gene Panel, Blood test. LQTS is a genetic cardiac disorder characterized by QT prolongation and T-wave abnormalities on EKG, and may result in recurrent syncope, ventricular arrhythmia, and sudden cardiac death. Romano-Ward syndrome (RWS), which accounts for the majority of LQTS, follows an autosomal dominant inheritance pattern and is caused by pathogenic variants in genes that encode cardiac ion channels or associated proteins. The diagnosis of RWS is established by the prolongation of the QTc interval in the absence of other conditions or factors that may lengthen it, such as QT-prolonging drugs or structural heart abnormalities. Clinical factors such as a history of syncope and family history also contribute to the diagnosis of RWS. LQTS may also be associated with congenital profound bilateral sensorineural hearing loss, a condition known as Jervell and Lange-Nielsen syndrome (JLNS). JLNS is inherited in an autosomal recessive inheritance pattern and is caused by homozygous or compound heterozygous pathogenic variants in either the KCNH2 or KCNQ1 genes. Timothy syndrome (TS) is a multisystem disorder involving prolonged QT interval in association with congenital anomalies. TS is inherited in an autosomal dominant manner and usually occurs as a result of a de novo heterozygous variant in the CACNA1C gene. Genes associated with LQTS include AKAP9, ANK2, CACNA1C, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ5, KCNQ1, SCN4B, SCN5A, and SNTA1. Additional clinical information about LQTS can be found in MML's ID LQTGP / Long QT Syndrome Multi-Gene Panel, Blood test.

Useful For: Providing a postmortem genetic evaluation in the setting of sudden unexplained death and suspicion for long QT or Brugada syndrome Identification of a pathogenic variant in the decedent, which may assist with risk assessment and predictive testing of at-risk family members

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values:
An interpretive report will be provided.


**Postmortem Cardiomyopathy Panel**

**Clinical Information:** Sudden cardiac death (SCD) is estimated to occur at an incidence of between 50 to 100 per 100,000 individuals in North America and Europe each year, claiming between 250,000 and 450,000 lives in the United States annually. In younger individuals (ages 15-35), the incidence of SCD is between 1 to 2 per 100,000 young individuals. Sudden cardiac death, particularly in young individuals, may suggest an inherited form of heart disease. In some cases of sudden cardiac death, autopsy may identify a structural abnormality such as a form of cardiomyopathy. Postmortem diagnosis of a hereditary cardiomyopathy may assist in confirmation of the cause and manner of death, as well as risk assessment in living family members. The cardiomyopathies are a group of disorders characterized by disease of the heart muscle. Cardiomyopathies are often caused by inherited, genetic, factors. When the identified structural or functional abnormality observed in a patient cannot be explained by acquired causes, genetic testing is commonly employed to identify a genetic underpinning. Overall, the cardiomyopathies are some of the most common genetic disorders. The inherited forms of cardiomyopathy include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic cardiomyopathy (ARVC or AC), and left ventricular noncompaction (LVNC). HCM is characterized by left ventricular hypertrophy in the absence of other causes, such as structural abnormalities, systemic hypertension, or physiologic hypertrophy due to rigorous athletic training (so-called "athlete's heart"). The incidence of HCM in the general population is approximately 1 in 500, and is most often caused by variants in genes encoding the components of the cardiac sarcomere. The clinical presentation of HCM can be variable, even within the same family. HCM can be asymptomatic in some individuals who harbor pathogenic HCM-associated variants, but can cause life-threatening arrhythmias that increase the risk of sudden cardiac death in other individuals. DCM is established by the presence of left ventricular enlargement and systolic dysfunction. DCM may present with heart failure with symptoms of congestion, arrhythmias or conduction system disease, or thromboembolic disease (stroke). The incidence of DCM is likely higher than originally reported due to subclinical phenotypes and underdiagnosis, with recent estimates suggesting that DCM affects approximately 1 in every 250 people. After exclusion of nongenetic causes such as ischemic injury, DCM is traditionally referred to as "idiopathic" dilated cardiomyopathy. Approximately 20% to 50% of individuals with idiopathic DCM may have an identifiable genetic cause for their disease. Families with 2 or more affected individuals are diagnosed with familial dilated cardiomyopathy. Arrhythmogenic cardiomyopathy (also referred to as arrhythmogenic right ventricular cardiomyopathy/dyplasia) (ARVD or AC) is characterized by replacement of the muscle tissue with fibrofatty tissue, resulting in an increased risk of arrhythmia and sudden death. Age of onset and severity are variable, but symptoms typically develop in adulthood. The incidence of AC is approximately 1 in 1,000 to 1 in 2,500. LVNC is characterized by left ventricular hypertrophy and prominent trabeculations of the ventricular wall, giving a spongy appearance to the muscle wall. It is thought to be caused by the arrest of normal myocardial morphogenesis. Clinical presentation is highly variable, ranging from no symptoms to congestive heart failure and life-threatening arrhythmias. An increased risk of thromboembolic events is also present with LVNC. Approximately 67% of LVNC is considered familial. Restrictive cardiomyopathy (RCM) is the rarest form of cardiomyopathy and is associated with abnormally rigid ventricular walls. Systolic function can be normal or near normal, but diastolic dysfunction is present. There are several nongenetic causes of RCM, but this condition can be familial as well, with the TNNI3 gene accounting for the majority of inherited cases. The age at presentation for familial RCM ranges from childhood to adulthood, and there is an increased risk of sudden death associated with this condition. Noonan syndrome is an autosomal dominant disorder of variable expressivity characterized by short stature, congenital heart defects, and characteristic facial...
dysmorphology. HCM is present in approximately 20% to 30% of individuals affected with Noonan syndrome. There are a number of disorders with significant phenotypic overlap with Noonan syndrome, including Costello syndrome, cardiofaciocutaneous (CFC) syndrome, and multiple lentigines syndrome (formerly called LEOPARD syndrome). Noonan syndrome and related disorders (also called the RASopathies) are caused by variants in genes involved in the RAS-MAPK signaling pathway. In some cases, variants in these genes may cause cardiomyopathy in the absence of other syndromic features. Cardiomyopathy may also be caused by an underlying disease such as a mitochondrial disorder, a muscular dystrophy, or a metabolic storage disorder. In these cases, heart disease may be the first feature to come to attention clinically. The hereditary forms of cardiomyopathy are most frequently associated with an autosomal dominant form of inheritance, however X-linked and autosomal recessive forms of disease are also present. In some cases, compound heterozygous or homozygous variants may be present in genes typically associated with autosomal dominant inheritance, often leading to a more severe phenotype. Digenic variants (2 different heterozygous variants at separate genetic loci) in autosomal dominant genes have also been reported to occur in patients with severe disease (particularly HCM and ARVC). The inherited cardiomyopathies display both allelic and locus heterogeneity, whereby a single gene may cause different forms of cardiomyopathy (allelic heterogeneity) and variants in different genes can cause the same form of cardiomyopathy (locus heterogeneity). This comprehensive cardiomyopathy panel includes sequence analysis of 55 genes and may be considered for individuals with HCM, DCM, AC, or LVNC, whom have had uninformative test results from a more targeted, disease-specific test. This test may also be helpful when the clinical diagnosis is not clear, or when there is more than 1 form of cardiomyopathy in the family history. It is important to note that the number of variants of uncertain significance detected by this panel may be higher than for the disease-specific panels, making clinical correlation more difficult. Genes included in the Postmortem Cardiomyopathy Panel Gene Protein Inheritance Disease Association ABCC9 ATP-binding cassette, subfamily C, member 9 AD DCM, Cantu syndrome ACTC1 Actin, alpha, cardiac muscle AD CHD, DCM, HCM, LVNC ACTN2 Actinin, alpha-2 AD DCM, HCM ANKR1D Ankyrin repeat domain-containing protein 1 AD HCM, DCM BRAF V-RAF murine sarcoma viral oncogene homolog B1 AD Noonan/CFC/Costello syndrome CAV3 Caveolin 3 AD, AR HCM, LQTS, LGMD, Tateyama-type distal myopathy, rippling muscle disease CAS-BR-M murine ecotopic retroviral transforming sequence homolog AD Noonan-like syndrome disorder CRYAB Crystallin, alpha-B AD, AR DCM, myofibrillar myopathy CSR3 Cysteine-and glycine-rich protein 3 AD HCM, DCM DES Desmin AD, AR DCM, AC, myofibrillar myopathy, RVCM with AV block, neurogenic scapuloperoneal syndrome Kaeser type, LGMD DSC2 Desmocollin 2 AD, AR AC, ARVC + skin and hair findings DSG2 Desmoglein 2 AC AD, AR AC, DCM, Carvajal syndrome DTNA Dystrobrevin, alpha AD LVNC, CHD GLA Galactosidase, alpha X-linked Fabry disease HRAS V-HA-RAS Harvey rat sarcoma viral oncogene homolog AD Costello syndrome JUP Junction plakoglobin AD, AR AC, Naxos disease KRAS V-KI-RAS2 Kirsten rat sarcoma viral oncogene homolog AD Noonan/CFC/Costello syndrome LAMA4 Laminin, alpha-4 AD DCM LAMP2 Lysosome-associated member protein 2 X-linked Danon disease LDB3 LIM domain-binding 3 AD DCM, LVNC, myofibrillar myopathy LMNA Lamin A/C AD, AR DCM, EMD, LGMD, congenital muscular dystrophy (see OMIM for full listing) MAP2K1 Mitogen-activated protein kinase kinase 1 AD Noonan/CFC MAP2K2 Mitogen-activated protein kinase kinase 2 AD Noonan/CFC MYBPC3 Myosin-binding protein-C, cardiac AD HCM, DCM MYH6 Myosin, heavy chain 6, cardiac muscle, alpha HCM, DCM MYH7 Myosin, heavy chain 7, cardiac muscle, beta AD HCM, DCM, LVNC, myopathy MYL2 Myosin, light chain 2, regulatory, cardiac, slow AD HCM MYL3 Myosin, light chain 3, alkali, ventricular, skeletal, slow AD, AR HCM MYLK2 Myosin light chain kinase 2 AD HCM MYOZ2 Myozinien 2 AD HCM MYPN Myopalladin AD HCM, DCM NEXN Nexlin AD HCM, DCM NRAS Neuroblastoma RAS viral oncogene homolog AD Noonan syndrome PKP2 Plakophilin 2 AD AC PLN Phospholamban AD HCM, DCM PRKAG2 Protein kinase, AMP-activated, noncatalytic, gamma2 AD HCM, Wolff-Parkinson-White syndrome PTPN11 Protein-tyrosine phosphatase, nonreceptor-type, 11 AD Noonan/CFC/LEOPARD syndrome RAFL1 V-RAF-1 murine leukemia viral oncogene homolog 1 AD Noonan/LEOPARD syndrome RBM20 RNA-binding motif protein 20 AD DCM RYR2 Ryanodine receptor 2 AD AC, CPVT, LQTS SCN5A Sodium channel, voltage gated, type V, alpha subunit AD Brugada syndrome, DCM, heart block, LQTS, SSS, SIDS SCD Sarco glycan, delta AD, AR DCM, LGMD SHOC2 Suppressor of clear, C. elegans, homolog of AD Noonan- like syndrome with loose anagen hair SOS1 Son of sevenless, droposphil, homolog 1 AD Noonan syndrome TAZ Tafazzin X-linked Barth syndrome, LVNC, DCM TCPAP Titin-cap (telethonin) AD, AR HCM, DCM, LGMD TMEM43 Transmembrane protein 43 AD AC, EMD TNN1 Troponin C, slow AD HCM, DCM TNN3 Troponin I, cardiac AD, AR DCM, HCM, RVCM TTN2 Troponin T2, cardiac AD HCM, DCM, RVCM,
LVNC TPM1 Tropomyosin 1 AD HCM, DCM, LVNC TTN Titin AD, AR HCM, DCM, ARVC, myopathy TTR Transthyretin AD Transthyretin-related amyloidosis VCL Vinculin AD HCM, DCM
Abbreviations: Hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic cardiomyopathy (AC), left ventricular noncompaction cardiomyopathy (LVNC), restrictive cardiomyopathy (RCM), limb-girdle muscular dystrophy (LGMD), Emory muscular dystrophy (EMD), congenital heart defect (CHD), sudden infant death syndrome (SIDS), long QT syndrome (LQTS), sick sinus syndrome (SSS), autosomal dominant (AD), autosomal recessive (AR)

Useful For: Providing a comprehensive postmortem genetic evaluation in the setting of sudden unexplained death or with a personal or family history suggestive of hereditary cardiomyopathy
Identification of a pathogenic variant in the decedent, which may assist with risk assessment and predictive testing of at-risk family members

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values:
An interpretive report will be provided.

of aortic aneurysm/dissection may assist in confirmation of the cause of death, as well as risk assessment in living family members. Marfan syndrome (MFS) is an autosomal dominant genetic disorder affecting the connective tissue and occurs in approximately 1 to 2 per 10,000 individuals. It is characterized by the presence of skeletal, ocular, and cardiovascular manifestations and is caused by variants in the FBN1 gene. Skeletal findings may include tall stature, chest wall deformity, scoliosis, and joint hypermobility. Lens dislocation (ectopia lentis) is the cardinal ocular feature, and aortic root dilatation/dissection and mitral valve prolapse are the main cardiovascular features. Diagnosis is based on the revised Ghent nosology and genetic testing of FBN1. Management aims to monitor and slow the rate of aortic root dilatation, and initiate appropriate medical and/or surgical intervention as needed. Other phenotypes associated with the FBN1 gene include autosomal dominant ectopia lentis (displacement of the lens of the eye), familial thoracic aortic aneurysm and dissections (TAAD), isolated skeletal features of MFS, MASS phenotype (mitral valve prolapse, aortic diameter increased, stretch marks, skeletal features of MFS), Shprintzen-Goldberg syndrome (Marfanoid-craniosynostosis; premature ossification and closure of sutures of the skull), and autosomal dominant Weill-Marchesani syndrome (short stature, short fingers, ectopia lentis). Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disease with significant overlap with Marfan syndrome, but may include involvement of other organ systems and is primarily caused by variants in TGFBR1 and TGFBR2. Features of LDS that are not typical of MFS include craniofacial and neurodevelopmental abnormalities and arterial tortuosity with increased risk for aneurysm and dissection throughout the arterial tree. Variants in the SMAD3 gene have been reported in families with a LDS-like phenotype with arterial aneurysms and tortuosity and early onset osteoarthritis. Thoracic aortic aneurysm and dissections (TAAD) is a genetic condition primarily involving dilatation and dissection of the thoracic aorta, but may also include aneurysm and dissection of other arteries. TAAD has a highly variable age of onset and presentation, and may involve additional features such as congenital heart defects and other features of connective tissue disease or smooth muscle abnormalities depending on the causative gene. The gene most commonly involved in familial TAAD is ACTA2, followed by TGFBR1 and TGFBR2, and MYH11. Variants in the MYLK gene have been reported in a small subset of families with familial TAAD. TGBF2 variants have also been reported in families with TAAD and systemic features that overlap with LDS and MFS. The COL3A1 gene causes Ehlers Danlos syndrome type IV (vascular type), an autosomal dominant connective tissue disease with characteristic facial features, thin, translucent skin, easy bruising, and arterial, intestinal, and uterine fragility. Arterial rupture may be preceded by aneurysm or dissection, or may occur spontaneously. Autosomal dominant variants of the FBN2 gene are known to cause congenital contractual arachnodactyly (CCA), which has several overlapping features with Marfan syndrome, including dolichostenomelia, scoliosis, pectus deformity, arachnodactyly, and a risk for thoracic aortic aneurysm. Variants of the CBS gene cause homocystinuria an autosomal recessive disorder of amino acid metabolism with clinical overlap with Marfan syndrome; including lens dislocation and skeletal abnormalities, as well as increased risk for abnormal blood clotting. Variants in the SKI gene cause Shprintzen-Goldberg syndrome (SGS), an autosomal dominant condition with overlap with LDS and MFS. Distinguishing features of SGS include hypotonia and intellectual disability. Aortic root dilatation is less frequent in SGS than in LDS or MFS but, when present, it can be severe. Homozygous and compound heterozygous loss of function variants in the SLC2A10 gene have been described in arterial tortuosity syndrome, a condition characterized by generalized tortuosity and elongation of all major arteries in addition to other connective tissue disease features. Many of these described disorders have distinct genetic causes but may present phenotypically similarly, leading to difficulty in accurate diagnosis. However, gene-based management strategies have been described for some of these disorders. Therefore, comprehensive genetic analysis may be useful for accurate diagnosis and gene-based management. Genes included in Postmortem Marfan and Related Panel: Gene Protein Inheritance Known Association ACTA2 Actin, alpha-2, smooth muscle, aorta AD TAAD CBS Cystathionine beta-synthase AR Homocystinuria COL3A1 Collagen, type III, alpha-1 AD Ehlers-Danlos syndrome type IV (vascular type) FBN1 Fibrillin 1 AD Marfan syndrome/TAAD ectopia lentis/ MASS phenotype/Shprintzen-Goldberg syndrome/Weill-Marchesani syndrome FBN2 Fibrillin 2 AD Congenital contractual arachnodactyly MYH11 Myosin, heavy chain 11, smooth muscle AD TAAD MYLK Myosin light chain kinase AD TAAD SKI V-SKI avian sarcoma viral oncogene homolog AD Shprintzen-Goldberg syndrome SLC2A10 Solute carrier family 2 (facilitated glucose transporter), member 10 AR Arterial Tortuosity syndrome/TAAD (autosomal recessive) SMAD3 Mothers against decapentaplegic, drosophila, homolog of, 3 AD Loeys-Dietz syndrome/TAAD TGFBR2 Transforming growth factor, beta-2 AD TAAD TGFBR1 Transforming growth factor-beta receptor, type I AD Loeys-Dietz syndrome/TAAD TGFBR2 Transforming growth factor-beta receptor, type II AD Loeys-Dietz syndrome/TAAD
Useful For: Providing a comprehensive postmortem genetic evaluation in the setting of a sudden death attributed to thoracic aortic dissection or with a personal or family history suggestive of Marfan syndrome, Loeys-Dietz syndrome, thoracic aortic aneurysm and dissections, or a related disorder. Identification of a pathogenic variant in the decedent, which may assist with risk assessment and predictive testing of at-risk family members.

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values: An interpretive report will be provided.


Postmortem Noonan and Related Panel

Clinical Information: Noonan syndrome (NS) is an autosomal dominant disorder of variable expressivity whose characteristic features can include short stature, congenital heart defects, characteristic facial dysmorphism, unusual chest shape, developmental delay of varying degree, cryptorchidism, and coagulation defects, among other features. In approximately 20% to 30% of cases, Noonan syndrome and related disorders are associated with hypertrophic cardiomyopathy, which may lead to sudden cardiac death. Postmortem diagnosis of Noonan syndrome or a related disorder may assist in confirmation of the
cause of death, as well as risk assessment in living family members. Other heart defects associated with Noonan syndrome and related disorders include pulmonary valve stenosis (20%-50%), atrial septal defects (6%-10%), ventricular septal defects (approximately 5%), and patent ductus arteriosus (approximately 3%). Facial features, which tend to change with age, may include hypertelorism, downward-slanting eyes, epicanthal folds, and low-set and posteriorly rotated ears. Mild mental retardation is seen in up to one-third of adults. The incidence of NS is estimated to be between 1 in 1,000 and 1 in 2,500, although subtle expression in adulthood may cause this number to be an underestimate.

NS is genetically heterogeneous, with 4 genes currently associated with the majority of cases: PTPN11, RAF1, SOS1, and KRAS. Heterozygous variants in NRAS, HRAS, BRF1, SHOC2, MAP2K1, MAP2K2, and CBL have also been associated with a smaller percentage of NS and related phenotypes. All of these genes are involved in a common signal transduction pathway known as the Ras-mitogen-activated protein kinase (MAPK) pathway. The MAPK pathway is important for cell growth, differentiation, senescence, and death. Molecular genetic testing of all of the known genes identifies a pathogenic variant in approximately 75% of affected individuals. NS can be sporadic and due to new (de novo) variants; however, an affected parent can be recognized in 30% to 75% of families. Some studies have shown that there is a genotype-phenotype correlation associated with NS. An analysis of a large cohort of individuals with NS has suggested that PTPN11 variants are more likely to be found when pulmonary stenosis is present, while hypertrophic cardiomyopathy is commonly associated with RAF1 variants, but rarely associated with PTPN11. A number of related disorders exist that have phenotypic overlap with NS and are caused by variants in the same group of genes. PTPN11 and RAF1 variants have been associated with LEOPARD (lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and deafness) syndrome, an autosomal dominant disorder sharing several clinical features with NS. Variants in BRF1, MAP2K1, MAP2K2, and KRAS have been identified in individuals with cardiofaciocutaneous (CFC) syndrome, a condition involving congenital heart defects, cutaneous abnormalities, Noonan-like facial features, and severe psychomotor developmental delay. Costello syndrome, which is characterized by coarse facies, short stature, distinctive hand posture and appearance, severe feeding difficulty, failure to thrive, cardiac anomalies, and developmental disability has been primarily associated with variants in HRAS. Variation in SHOC2 has been associated with a distinctive phenotype involving features of Noonan syndrome and loose anagen hair. Genes included in the Postmortem Noonan and Related Panel Gene Inheritance Disease Association BRF1 V-RAF murine sarcoma viral oncogene homolog b1 AD Noonan/CFC/Costello syndrome CBL CAS-BR-M murine ecotropic retroviral transforming sequence homolog AD Noonan-like syndrome disorder HRAS V-HA-RAS Harvey rat sarcoma viral oncogene homolog AD Costello syndrome KRAS V-KI-RAS Kirsten rat sarcoma viral oncogene homolog AD Noonan/CFC/Costello syndrome MAP2K1 Mitogen-activated protein kinase, kinase 1 AD Noonan/CFC MAP2K2 Mitogen-activated protein kinase, kinase 2 AD Noonan/CFC NRAS Neuroblastoma ras viral oncogene homolog AD Noonan syndrome PTPN11 Protein-tyrosine phosphatase, nonreceptor-type, 11 AD Noonan/CFC/LEOPARD syndrome RAF1 V-raf-1 murine leukemia viral oncogene homolog 1 AD Noonan/LEOPARD syndrome SHOC2 Suppressor of clear, c. Elegans, homolog of AD Noonan-syndrome like with loose anagen hair SOS1 Son of sevenless, drosophila, homolog 1 AD Noonan- like syndrome with loose anagen hair Abbreviations: autosomal dominant (AD)

**Useful For:** Providing a comprehensive postmortem genetic evaluation in the setting of sudden cardiac death and suspicion for Noonan syndrome or related disorders. Identification of a pathogenic variant in the decedent, which may assist with risk assessment and predictive testing of at-risk family members

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.
testing is particularly recommended under the following circumstances (risk factors): - Family history of sudden infant death syndrome or other sudden unexpected deaths at any age - Family history of Reye syndrome - Maternal complications of pregnancy (acute fatty liver pregnancy, HELLP syndrome [hemolysis, elevated liver enzymes, and low platelet count]) - Lethargy, vomiting, fasting in the 48 hours prior to death - Allegation of child abuse (excluding obvious cases of trauma, physical harm) - Macroscopic findings at autopsy: - Fatty infiltration of the liver - Dilated or hypertrophic cardiomyopathy - Autopsy evidence of infection that routinely would not represent a life-threatening event

**Interpretation:** Reports of abnormal acylcarnitine profiles will include an overview of the results and of their significance, a correlation to available clinical information, possible differential diagnoses, recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis) as indicated, name and phone number of contacts who may provide these studies at Mayo Clinic or elsewhere, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions. Abnormal results are not always sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis based on an acylcarnitine analysis, independent biochemical (eg, FAO / Fatty Acid Oxidation Probe Assay, Fibroblast Culture) or molecular genetic analyses are required using additional tissue such as skin fibroblasts from the deceased patient. If not available, molecular genetic analysis of a patient's parents may enable the confirmation of a diagnosis.

**Reference Values:**
Quantitative results are compared to a constantly updated range which corresponds to the 5 to 95 percentile interval of all postmortem cases analyzed in our laboratory.

**Clinical References:**

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**Potassium, 24 Hour, Urine**

**Clinical Information:** Potassium (K+) is the major intracellular cation. Functions of potassium include regulation of neuromuscular excitability, heart contractility, intracellular fluid volume, and hydrogen ion concentration. The physiologic function of K+ requires that the body maintain a low extracellular fluid (ECF) concentration of the cation; the intracellular concentration is 20 times greater than the extracellular K+ concentration. Only 2% of total body K+ circulates in the plasma. The kidneys provide the most important regulation of K+. The proximal tubules reabsorb almost all the filtered K+. Under the influence of aldosterone, the remaining K+ can then be secreted into the urine in exchange for sodium in both the collecting ducts and the distal tubules. Thus, the distal nephron is the principal determinant of urinary K+ excretion. Decreased excretion of K+ in acute renal disease and end-stage renal failure are common causes of prolonged hyperkalemia. Renal losses of K+ may occur during the diuretic (recovery) phase of acute tubular necrosis, during administration of nonpotassium sparing diuretic therapy, and during states of excess mineralocorticoid or glucocorticoid.

**Useful For:** Determining the cause for hyper- or hypokalemia

**Interpretation:** Hypokalemia reflecting true total body deficits of potassium (K+) can be classified into renal and nonrenal losses based on the daily excretion of K+ in the urine. During hypokalemia, if urine excretion of K+ is below 30 mEq/day, it can be concluded that renal reabsorption of K+ is appropriate. In this situation, the causes for the hypokalemic state are either decreased K+ intake or extra renal loss of K+ rich fluid. Urine excretion of more than 30 mEq/d in a hypokalemia setting is inappropriate and indicates that the kidneys are the primary source of the lost K+.
**Potassium, Body Fluid**

**Clinical Information:** Potassium (K+) is the major cation of the intracellular fluid. Disturbance of potassium homeostasis has serious consequences. Decrease in extracellular potassium is characterized by muscle weakness, irritability, paralysis, fast heart rate, specific cardiac conduction effects that are apparent by electrocardiographic examination, and eventual cardiac arrest. More than 90% of hypertensive patients with aldosteronism have a hypokalemia (low K+). Low K(+) also is common in vomiting, diarrhea, alcoholism, and folic acid deficiency. Abnormally high extracellular K+ levels produce symptoms of mental confusion; weakness, numbness and tingling of the extremities; weakness of the respiratory muscles; flaccid paralysis of the extremities; slowed heart rate, and eventually peripheral vascular collapse and cardiac arrest. Hyperkalemia may be seen in end stage renal failure, hemolysis, trauma, Addison's disease, metabolic acidosis, acute starvation, dehydration, and with rapid K(+) infusion.

**Useful For:** Measurement of serum potassium is used for evaluation of electrolyte balance, cardiac arrhythmia, muscular weakness, hepatic encephalopathy, and renal failure. Potassium should be monitored during treatment of many conditions but especially in ketoacidosis of diabetes mellitus and any intravenous therapy for fluid replacement.

**Interpretation:** Plasma K=values less than 3.0 mEq/L are associated with marked neuromuscular symptoms and are evidence of a critical degree of intracellular depletion. K(+) values < 2.5 mEq/L are potentially life-threatening.

**Reference Values:** Not applicable

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**Potassium, Random, Urine**

**Clinical Information:** Potassium (K+) is the major intracellular cation. Functions of K+ include regulation of neuromuscular excitability, heart contractility, intracellular fluid volume, and hydrogen ion concentration. The physiologic function of K+ requires that the body maintain a low extracellular fluid (ECF) concentration of the cation; the intracellular K+ concentration is 20 times greater than the extracellular concentration. Only 2% of total body K+ circulates in the plasma. The kidneys provide the most important regulation of K+. The proximal tubules reabsorb almost all the filtered K+. Under the influence of aldosterone, the remaining K+ can then be secreted into the urine in exchange for sodium in both the collecting ducts and the distal tubules. Thus, the distal nephron is the principal determinant of urinary K+ excretion. Decreased excretion of K+ in acute renal disease and end-stage renal failure are common causes of prolonged hyperkalemia. Renal losses of K+ may occur during the diuretic (recovery) phase of acute tubular necrosis, during administration of nonpotassium sparing diuretic therapy, and during states of excess mineralocorticoid or glucocorticoid.

**Useful For:** Determining the cause for hyper- or hypokalemia

**Interpretation:** Hypokalemia reflecting true total body deficits of potassium (K+) can be classified into renal and nonrenal losses based on the daily excretion of K+ in the urine. During hypokalemia, if urine excretion of K+ is less than 30 mEq/d, it can be concluded that renal reabsorption of K+ is appropriate. In this situation, the causes for the hypokalemic state are either decreased K+ intake or extra renal loss of K+ rich fluid. Urine excretion of more than 30 mEq/d in a hypokalemia setting is inappropriate and indicates that the kidneys are the primary source of the lost K+.

**Reference Values:**
No established reference values


**Potassium, Serum**

**Clinical Information:** Potassium is the major cation of the intracellular fluid. Disturbance of potassium homeostasis has serious consequences. Decreases in extracellular potassium are characterized by muscle weakness, irritability, and eventual paralysis. Cardiac effects include tachycardia, other cardiac conduction abnormalities that are apparent by electrocardiographic examination, and eventual cardiac arrest. Hypokalemia (low potassium) is common in vomiting, diarrhea, alcoholism, and folic acid deficiency. Additionally, >90% of hypertensive patients with aldosteronism have hypokalemia. Abnormally high extracellular potassium levels produce symptoms of mental confusion; weakness, numbness and tingling of the extremities; weakness of the respiratory muscles; flaccid paralysis of the extremities; slowed heart rate; and eventually peripheral vascular collapse and cardiac arrest. Hyperkalemia may be seen in end-stage renal failure, hemolysis, trauma, Addison's disease, metabolic acidosis, acute starvation, dehydration, and with rapid potassium infusion.

**Useful For:** Evaluation of electrolyte balance, cardiac arrhythmia, muscular weakness, hepatic encephalopathy, and renal failure. Potassium should be monitored during treatment of many conditions but especially in diabetic ketoacidosis and any intravenous therapy for fluid replacement.

**Interpretation:** Potassium levels <3.0 mmol/L are associated with marked neuromuscular symptoms and are evidence of a critical degree of intracellular depletion. Potassium levels <2.5 mmol/L are potentially life-threatening. High potassium can be an acute medical emergency, particularly if the potassium increases over a short period of time. At values >6.0 mmol/L, symptoms are typically apparent. Potassium levels >6.0 mmol/L are potentially life-threatening. Levels >10.0 mmol/L are, in most cases, fatal.

**Reference Values:**
> or =12 months: 3.6-5.2 mmol/L

Reference values have not been established for patients that are less than 12 months of age.


**Potato White IgG**

**Interpretation:** mcg/mL of IgG

- Lower Limit of Quantitation*: 2.0
- Upper Limit of Quantitation**: 200

**Reference Values:**
<2 mcg/mL.

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.
Interpretation: Beef IgG <2.0 mcg/mL Chicken IgG <2.0 mcg/mL Egg White IgG <2.0 mcg/mL Egg Yolk IgG <2.0 mcg/mL Lamb/Mutton IgG <2.0 mcg/mL Pork IgG <2.0 mcg/mL Turkey IgG <2.0 mcg/mL. The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Reference Values:
<2.0 mcg/mL

PPOXZ 35530

PPOX Gene, Full Gene Analysis

Clinical Information: Variegate porphyria (VP) is an autosomal dominant (AD) cutaneous porphyria that can present with or without acute attacks that phenocopy acute intermittent porphyria (AIP). The most common clinical presentation of VP is increased photosensitivity, blistering, hyperpigmentation, and skin fragility in sun-exposed areas. The acute attacks of VP can include abdominal pain, vomiting, diarrhea, constipation, urinary retention, acute episodes of neuropathic symptoms, psychiatric symptoms, seizures, respiratory paralysis, tachycardia, and hypertension. Respiratory paralysis can progress to coma and death. Cutaneous manifestations include edema, sun-induced erythema, acute painful photodermatitis, and urticaria. In some cases patients present with isolated photosensitivity. Variegate porphyria is caused by mutations in the PPOX gene. Mutations are typically inherited in an autosomal dominant fashion with incomplete penetrance, although homozygous mutations have been reported in association with a more severe clinical phenotype in early childhood. Acute attacks may be prevented by avoiding both endogenous and exogenous triggers. These triggers include porphyrogenic drugs, hormonal contraceptives, fasting, alcohol, tobacco, and cannabis. Fecal porphyrins analysis and quantitative urinary porphyrins analysis are helpful in distinguishing variegate porphyria from AIP and hereditary coproporphyria.

Useful For: Confirmation of variegate porphyria for patients with clinical and biochemical features of the disease Identification of familial PPOX mutation to allow for genetic testing in family members

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

PWAS 35535

Prader-Willi/Angelman Syndrome, Molecular Analysis

Clinical Information: Prader-Willi syndrome (PWS) is a congenital disorder characterized by a biphasic clinical course. Neonates with PWS are hypotonic, have a weak cry, and are poor feeders, but improve over time. In later infancy and childhood, individuals with PWS have global developmental delay, short stature, hypogonadism, small hands and feet, and marked hyperphagia leading to obesity. PWS is thought to be due to loss of function of paternally expressed genes, although specific genes have not yet been definitively implicated in the phenotype of PWS. Etiology of Prader-Willi syndrome:
-Chromosome 15 deletion (15q11-13): approximately 70%-75%
-Maternal uniparental disomy (UPD):
20%-30% -Imprinting defect: 1%-5% -Chromosome rearrangement: rare The phenotype caused by paternal deletions of 15q11-13 and by maternal UPD are generally identical with the exception of relative hypopigmentation being more common in patients with deletion PWS. Angelman syndrome (AS) is a nonprogressive congenital disorder characterized by more significant developmental delay and mental retardation, ataxia, seizures, jerky arm movements, macrostomia, tongue thrusting, unprovoked laughter, brachycephaly, and virtual absence of speech. AS is due to loss of function of the maternally expressed gene UBE3A. Etiology of Angelman syndrome: -Chromosome 15 deletion (15q11-13): approximately 70%-75% -Paternal UPD: approximately 5% -UBE3A mutation: approximately 10% -Imprinting defect: 2%-5% -Chromosome rearrangement: rare -Unknown: approximately 10% The phenotype of AS patients with maternal deletions is generally more severe than that associated with paternal UPD or imprinting defects, including a higher rate or severity of microcephaly, seizures, and motor difficulties. Patients with AS caused by paternal UPD or imprinting defects generally show better growth and higher developmental and language abilities. Both chromosome 15 deletions and UPD most often occur as de novo events during conception and, thus, recurrence risk to siblings is very low. In rare cases, chromosome 15 deletions and UPD occur as a result of parental translocations or other rare cytogenetic rearrangements, and in these cases recurrence risks to siblings are increased. The recurrence risk associated with imprinting defects is dependent on whether or not there is an identifiable mutation. UBE3A mutations can occur sporadically or be inherited in an autosomal dominant fashion. There is a 50% recurrence risk to siblings in cases of an inherited UBE3A mutation. Due to the complex genetic etiology of PWS and AS and the corresponding variability in recurrence risks, careful cytogenetic and molecular testing and family assessment are necessary to provide accurate genetic counseling. Initial studies to rule-out PWS or AS should include chromosomal microarray analysis to identify chromosome abnormalities that may have phenotypic overlap with PWS or AS, and methylation-sensitive multiple ligation-dependent probe amplification (MLPA) to identify deletions, duplications, and methylation defects. In cases where methylation-sensitive MLPA suggests either deletion or duplication, FISH can be used to confirm type I and type II deletions or characterize the disease mechanism, respectively. In cases where methylation-sensitive MLPA suggests abnormal methylation in the absence of a deletion or duplication, UPD studies can be used to characterize the disease mechanism. Assessment of patients found to have a deletion in the PWS/AS critical region on routine cytogenetic analysis or chromosomal microarray can include confirmation of the deletion by FISH analysis and MLPA analysis to define parent of origin. See Prader-Willi and Angelman Syndromes: Laboratory Approach to Diagnosis in Special Instructions for more information.

Useful For: Confirmation of diagnosis in patients suspected of having either Prader-Willi syndrome (PWS) or Angelman syndrome (AS) based on clinical assessment or previous laboratory analysis

Prenatal diagnosis in families at risk for PWS or AS

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.


Prealbumin (PAB), Serum

Clinical Information: Prealbumin is synthesized in the liver and acts as a binding protein for thyroxine and retinol-binding protein. The serum concentration of prealbumin reflects the synthesis capacity of the liver and is markedly diminished in malnutrition and other conditions. Due to its short half-life of approximately 2 days, prealbumin can be used for monitoring the nutritional status and

PALB 9005

Prealbumin (PAB), Serum

Clinical Information: Prealbumin is synthesized in the liver and acts as a binding protein for thyroxine and retinol-binding protein. The serum concentration of prealbumin reflects the synthesis capacity of the liver and is markedly diminished in malnutrition and other conditions. Due to its short half-life of approximately 2 days, prealbumin can be used for monitoring the nutritional status and
efficacy of parenteral nutrition.

**Useful For:** Assessing nutritional status, especially in monitoring the response to nutritional support in the acutely ill patient

**Interpretation:** Values of 0 to 5 mg/dL, 5 to 10 mg/dL, and 10 to 15 mg/dL indicate severe, moderate, and mild protein depletion.

**Reference Values:**
19-38 mg/dL

**Clinical References:**

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**Pregabalin, Serum**

**Clinical Information:** Pregabalin (Lyrica) is an anticonvulsant drug used to treat partial seizures in patients and is a more potent successor to gabapentin. Pregabalin is commonly used for neuropathic pain and fibromyalgia. This test can be used by physicians to assess compliance and may be clinically useful in patients with renal failure who generally require lower dosages. Therapeutic and toxic ranges are not well defined. Therapeutic concentrations are reported to be from 2 to 5 mcg/mL, while toxicity may occur at concentrations above 10 mcg/mL.

**Useful For:** Monitoring serum pregabalin (Lyrica) concentrations, assessing compliance, and adjusting dosage in patients.

**Interpretation:** The serum concentration should be interpreted in the context of the patient's clinical response and may provide useful information in patients showing poor response, noncompliance, or adverse effects.

**Reference Values:**
2.0-5.0 mcg/mL

**Clinical References:**

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**Pregnenolone and 17-Hydroxyprogrenolone**

**Clinical Information:** Congenital adrenal hyperplasia (CAH) is caused by inherited defects in steroid biosynthesis. Deficiencies in several enzymes cause CAH including 21-hydroxylase (CYP21A2 mutations; 90% of cases), 11-hydroxylase (CYP11A1 mutations; 5%-8%), 3-beta-hydroxy dehydrogenase (HSD3B2 mutations; <5%), and 17-alpha-hydroxylase (CYP17A1 mutations; 125 cases reported to date). The resulting hormone imbalances (reduced glucocorticoids and mineralocorticoids, and elevated steroid intermediates and androgens) can lead to life-threatening, salt-wasting crises in the newborn period and incorrect gender assignment of virilized females. The adrenal glands, ovaries, testes, and placenta produce steroid intermediates, which are hydroxylated at position 21 (by 21-hydroxylase) and position 11 (by 11-hydroxylase) to produce cortisol. Deficiency of either 21-hydroxylase or 11-hydroxylase results in decreased cortisol synthesis and loss of feedback inhibition of adrenocorticotropic hormone (ACTH) secretion. The consequent increased pituitary release of ACTH drives increased production of steroid intermediates. The steroid intermediates are oxidized at position 3 (by 3-beta-hydroxy dehydrogenase [3-beta-HSD]). The 3-beta-HSD enzyme allows formation of 17-hydroxyprogesterone (17-OHPG) from...
17-hydroxypregnenolone and progesterone from pregnenolone. When 3-beta-HSD is deficient, cortisol is decreased, 17-hydroxypregnenolone and pregnenolone levels may increase, and 17-OHPG and progesterone levels, respectively, are low. Dehydroepiandrosterone is also converted to androstenedione by 3-beta-HSD, and may be elevated in patients affected with 3-beta-HSD deficiency. The best screening test for CAH, most often caused by either 21- or 11-hydroxylase deficiency, is the analysis of 17-hydroxypregesterone (along with cortisol and androstenedione). CAH21 / Congenital Adrenal Hyperplasia (CAH) Profile for 21-Hydroxylase Deficiency allows the simultaneous determination of these 3 analytes. Alternately, these tests may be ordered individually; OHPG / 17-Hydroxypregesterone, Serum; CINP / Cortisol, Serum, LC-MS/MS; and ANST / Androstenedione, Serum. If both 21- and 11-hydroxylase deficiency have been ruled out, analysis of 17-hydroxypregnenolone and pregnenolone may be used to confirm the diagnosis of 3-beta-HSD or 17-alpha-hydroxylase deficiency. See Steroid Pathways in Special Instructions.

**Useful For:** An ancillary test for congenital adrenal hyperplasia (CAH), particularly in situations in which a diagnosis of 21-hydroxylase and 11-hydroxylase deficiency have been ruled out. Confirming a diagnosis of 3-beta-hydroxy dehydrogenase (3-beta-HSD) deficiency and 17-alpha-hydroxylase deficiency. Analysis for 17-hydroxypregnenolone is also useful as part of a battery of tests to evaluate females with hirsutism or infertility. Both can result from adult-onset CAH.

**Interpretation:** Diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always require the measurement of several steroids. Patients with CAH due to steroid 21-hydroxylase gene (CYP21A2) mutations usually have very high levels of androstenedione, often 5-fold to 10-fold elevations. 17-OHPG levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. For the HSD3B2 mutation, cortisol, 17-OHPG and progesterone levels will be will be decreased; 17-hydroxypregnenolone and pregnenolone and DHEA levels will be increased. In the much less common CYP11A1 mutation, androstenedione levels are elevated to a similar extent as seen in CYP21A2 mutation, and cortisol also is low, but 17-OHPG is only mildly, if at all, elevated. In the also very rare 17-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxypregnenolone, 17-OHPG, dehydroepiandrosterone sulfate), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid and its precursors (in particular pregnenolone, 11-deoxycorticosterone, corticosterone, and 18-hydroxycorticosterone) are increased. See Steroid Pathways in Special Instructions.

**Reference Values:**
PREGNENOLONE
CHILDREN*

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<td>Males</td>
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<td>0-6 years: not established</td>
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<tr>
<td>7-9 years: &lt;206 ng/dL</td>
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<td>10-12 years: &lt;152 ng/dL</td>
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<td>13-15 years: 18-197 ng/dL</td>
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<td>Tanner Stages</td>
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<td>Stage I: &lt;157 ng/dL</td>
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<td>Stage II: &lt;144 ng/dL</td>
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<td>Stage III: &lt;215 ng/dL</td>
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<td>Stage IV-V: 19-201 ng/dL</td>
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<td>Females</td>
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<td>0-6 years: not established</td>
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<tr>
<td>7-9 years: &lt;151 ng/dL</td>
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<tr>
<td>10-12 years: 19-220 ng/dL</td>
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<td>13-15 years: 22-210 ng/dL</td>
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<td>Tanner Stages</td>
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<tr>
<td>Stage I: &lt;172 ng/dL</td>
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<td>Stage II: 22-229 ng/dL</td>
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<td>Stage III: 34-215 ng/dL</td>
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<td>Stage IV-V: 26-235 ng/dL</td>
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ADULTS
> or =18 years: 33-248 ng/dL

17-HYDROXYPREGNENOLONE

CHILDREN*

Males
Premature (26-28 weeks): 1,219-9,799 ng/dL
Premature (29-36 weeks): 346-8,911 ng/dL
Full term (1-5 months): 229-3,104 ng/dL
6 months-364 days: 221-1,981 ng/dL
1-2 years: 35-712 ng/dL
3-6 years: <277 ng/dL
7-9 years: <188 ng/dL
10-12 years: <393 ng/dL
13-15 years: 35-465 ng/dL
16-17 years: 32-478 ng/dL

Tanner Stages
Stage I: <209 ng/dL
Stage II: <356 ng/dL
Stage III: <451 ng/dL
Stage IV-V: 35-478 ng/dL

Females
Premature (26-28 weeks): 1,219-9,799 ng/dL
Premature (29-36 weeks): 346-8,911 ng/dL
Full term (1-5 months): 229-3,104 ng/dL
6 months-364 days: 221-1,981 ng/dL
1-2 years: 35-712 ng/dL
3-6 years: <277 ng/dL
7-9 years: <213 ng/dL
10-12 years: <399 ng/dL
13-15 years: <408 ng/dL
16-17 years: <424 ng/dL

Tanner Stages
Stage I: <236 ng/dL
Stage II: <368 ng/dL
Stage III: <431 ng/dL
Stage IV-V: <413 ng/dL

ADULTS
Males
> or =18 years: 55-455 ng/dL
Females
> or =18 years: 31-455 ng/dL

Clinical References:
Pregnenolone, Serum

**Clinical Information:** Congenital adrenal hyperplasia (CAH) is caused by inherited defects in steroid biosynthesis. Deficiencies in several enzymes cause CAH including 21-hydroxylase (CYP21A2 mutations; 90% of cases), 11-hydroxylase (CYP11A1 mutations; 5%-8%), 3-beta-hydroxy dehydrogenase (HSD3B2 mutations; <5%), and 17-alpha-hydroxylase (CYP17A1 mutations; 125 cases reported to date). The resulting hormone imbalances (reduced glucocorticoids and mineralocorticoids, and elevated steroid intermediates and androgens) can lead to life-threatening, salt-wasting crises in the newborn period and incorrect gender assignment of virilized females. The adrenal glands, ovaries, testes, and placenta produce steroid intermediates, which are hydroxylated at position 21 (by 21-hydroxylase) and position 11 (by 11-hydroxylase) to produce cortisol. Deficiency of either 21-hydroxylase or 11-hydroxylase results in decreased cortisol synthesis and loss of feedback inhibition of adrenocorticotropic hormone (ACTH) secretion. The consequent increased pituitary release of ACTH drives increased production of steroid intermediates. The steroid intermediates are oxidized at position 3 (by 3-beta-hydroxy dehydrogenase [3-beta-HSD]). The 3-beta-HSD enzyme allows formation of 17-hydroxyprogesterone (17-OHPG) from 17-hydroxypregnenolone and progesterone from pregnenolone. When 3-beta-HSD is deficient, cortisol is decreased, 17-hydroxyprogrenenolone and pregnenolone levels may increase, and 17-OHPG and progesterone levels, respectively, are low. Dehydroepiandrosterone is also converted to androstenedione by 3-beta-HSD, and may be elevated in patients affected with 3-beta-HSD deficiency. The best screening test for CAH, most often caused by either 21- or 11-hydroxylase deficiency, is the analysis of 17-hydroxyprogesterone (along with cortisol and adrenocorticotropic hormone) secretion. The consequent increased pituitary release of ACTH drives increased production of steroid intermediates. The steroid intermediates are oxidized at position 3 (by 3-beta-hydroxy dehydrogenase [3-beta-HSD]). The 3-beta-HSD enzyme allows formation of 17-hydroxyprogesterone (17-OHPG) from 17-hydroxypregnenolone and progesterone from pregnenolone. When 3-beta-HSD is deficient, cortisol is decreased, 17-hydroxyprogrenenolone and pregnenolone levels may increase, and 17-OHPG and progesterone levels, respectively, are low. Dehydroepiandrosterone is also converted to androstenedione by 3-beta-HSD, and may be elevated in patients affected with 3-beta-HSD deficiency. The best screening test for CAH, most often caused by either 21- or 11-hydroxylase deficiency, is the analysis of 17-hydroxyprogesterone (along with cortisol and androstenedione). CAH21 / Congenital Adrenal Hyperplasia (CAH) Profile for 21-Hydroxylase Deficiency allows the simultaneous determination of these 3 analytes. Alternately, these tests may be ordered individually: OHPG / 17-Hydroxyprogesterone, Serum; CINP / Cortisol, Serum, LC-MS/MS; and ANST / Androstenedione, Serum. If both 21- and 11-hydroxylase deficiency have been ruled out, analysis of 17-hydroxypregnenolone and pregnenolone may be used to confirm the diagnosis of 3-beta-HSD or 17-alpha-hydroxylase deficiency. See Steroid Pathways in Special Instructions.

**Useful For:** An ancillary test for congenital adrenal hyperplasia, particularly in situations in which a diagnosis of 21-hydroxylase and 11-hydroxylase deficiency have been ruled out Confirming a diagnosis of 3-beta-hydroxy dehydrogenase deficiency

**Interpretation:** Diagnosis and differential diagnosis of congenital adrenal hyperplasia (CAH) always require the measurement of several steroids. Patients with CAH due to steroid 21-hydroxylase gene (CYP21A2) mutations usually have very high levels of androstenedione, often 5-fold to 10-fold elevations. 17-Hydroxyprogesterone (17-OHPG) levels are usually even higher, while cortisol levels are low or undetectable. All 3 analytes should be tested. For the HSD3B2 mutation, cortisol, 17-OHPG and progesterone levels will be will be decreased; 17-hydroxyprogrenenolone and pregnenolone and dehydroepiandrosterone levels will be increased. In the much less common CYP11A1 mutation, androstenedione levels are elevated to a similar extent as seen in CYP21A2 mutation, and cortisol also is low, but 17-OHPG is only mildly, if at all, elevated. In the also very rare 17-hydroxylase deficiency, androstenedione, all other androgen-precursors (17-alpha-hydroxyprogrenenolone, 17-OHPG, dehydroepiandrosterone sulfate), androgens (testosterone, estrone, estradiol), and cortisol are low, while production of mineral corticoid and its precursors (in particular pregnenolone, 11-deoxycorticosterone, corticosterone, and 18-hydroxycorticosterone) are increased. See Steroid Pathways in Special Instructions.

**Reference Values:**

**CHILDREN**

- **Males**
  - 0-6 years: not established
  - 7-9 years: <206 ng/dL
  - 10-12 years: <152 ng/dL

*Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  Page 1871*
13-15 years: 18-197 ng/dL
16-17 years: 17-228 ng/dL

Tanner Stages
Stage I: <157 ng/dL
Stage II: <144 ng/dL
Stage III: <215 ng/dL
Stage IV-V: 19-201 ng/dL

Females
0-6 years: not established
7-9 years: <151 ng/dL
10-12 years: 19-220 ng/dL
13-15 years: 22-210 ng/dL
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Tanner Stages
Stage I: <172 ng/dL
Stage II: 22-229 ng/dL
Stage III: 34-215 ng/dL
Stage IV-V: 26-235 ng/dL

ADULTS
> or =18 years: 33-248 ng/dL


Prenatal Aneuploidy Detection, FISH

Clinical Information: Approximately half of clinically recognizable spontaneous abortions have a major chromosomal anomaly. Up to 95% of chromosomal abnormalities diagnosed prenatally involve aneuploidy (gain or loss of whole chromosome) of chromosomes 13, 18, 21, X, and Y. In liveborn infants, about 8/1,000 have a major chromosome anomaly, of which 6.5/1,000 involve aneuploidy of the 5 chromosomes analyzed by this test. Therefore, aneuploidy of chromosomes 13, 18, 21, X, and Y accounts for 81% to 95% of major chromosome anomalies in liveborn infants. Techniques to detect aneuploidy include standard chromosome analysis and FISH. Standard chromosome analysis from amniotic fluid cells or chorionic villi requires 5 to 9 days for culture, harvest, and analysis. FISH, which uses DNA probes and can be performed on cultured and uncultured cells, can rapidly detect aneuploidy of 13, 18, 21, X, and Y in uncultured amniotic fluid cells or chorionic villi. FISH-based analysis may be helpful in medically urgent evaluations of newborn infants suspected to have aneuploidy of any of these chromosomes.

Useful For: Screening for chromosomal aneuploidies of chromosomes 13, 18, 21, X, and Y in prenatal specimens

Interpretation: An interpretive report is provided.

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An interpretive report will be provided.

**Clinical References:**

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**PHSP 5566**

**Prenatal Hepatitis Evaluation**

**Clinical Information:** Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. After a course of acute illness, HBV persists in about 10% of patients who were infected during adulthood. Some carriers are asymptomatic; others may develop chronic liver disease including cirrhosis and hepatocellular carcinoma. HBV is spread primarily through percutaneous contact with infected blood products (ie, blood transfusion, sharing of needles by drug addicts). The virus is found in virtually every type of human body fluid and also is spread through oral and genital contact. HBV can be transmitted from mother to child during delivery through contact with blood and vaginal secretions, but it is not commonly transmitted transplacentally. Infection of the infant can occur if the mother is a chronic hepatitis B surface antigen carrier or has an acute HBV infection at the time of delivery. Transmission is rare if an acute infection occurs in either the first or second trimester of pregnancy.

**Useful For:** Screening pregnant women for chronic hepatitis B
Determining the level of infectivity of chronic hepatitis B in pregnant women

**Interpretation:** Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum 6 to 16 weeks following hepatitis B virus (HBV) infection. A confirmed positive result for HBsAg is indicative of acute or chronic hepatitis B. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Persistence of HBsAg for more than 6 months indicates development of either a chronic carrier state or chronic liver disease. Hepatitis B surface antibody (anti-HBs) appears with the resolution of HBV infection after the disappearance of HBsAg. Hepatitis Be-antigen (HBeAg) appears at approximately the same time as HBsAg and indicates that the virus is replicating and the individual is infectious. Appearance of hepatitis Be antibody (anti-HBe) after the disappearance of HBsAg and HBeAg usually indicates recovery and loss of infectivity.

**Reference Values:**
Negative
See Viral Hepatitis Serologic Profiles in Special Instructions.

**Clinical References:**

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**PNZIK 65276**

**Prenatal Zika Virus IgM Antibody Capture MAC-ELISA, Serum**

**Clinical Information:** Zika virus is an RNA virus in the genus Flavivirus and is primarily transmitted through the bite of an infected Aedes species mosquito. Other means of transmission include through transfusion of blood and blood products, sexually through genital secretions, perinatally, vertically from mother to fetus, and potentially through contact with other body secretions such as tears and sweat. Historically, most cases of Zika virus infection have occurred in parts of Africa and South-East Asia. However, Zika virus emerged in South America in early 2015 and is now endemic in over 50 countries in South, Central, and North America, including in several US territories and focal regions of the southern United States. The majority (approximately 80%) of individuals infected with Zika virus are asymptomatic. Among symptomatic patients, fever, headache, retro-orbital pain, conjunctivitis, maculopapular rash, myalgias, and arthralgias are commonly reported. Notably, these symptoms can resolve without medical intervention.
symptoms are not distinct and can be seen with other emerging arboviruses, including dengue and chikungunya. Therefore, diagnostic testing for each of these viruses is recommended in patients returning for areas where these viruses cocirculate. Intrauterine or prenatal infection with Zika virus has been causally linked to development of microcephaly, with the greatest risk for fetal abnormality occurring if the infection is acquired during the first trimester. Finally, Zika virus has also been associated with development of Guillain-Barre syndrome. A number of Zika virus serologic and nucleic acid amplification tests (NAAT) have received emergency use authorization (EUA) through the FDA. The recommended tests vary by the patient's symptoms, course of illness, and whether or not the patient is pregnant. For the most up-to-date information regarding CDC testing guidelines visit www.cdc.gov/zika/. These guidelines are reflected in the following MML testing algorithms in Special Instructions: -Assessment for Zika Virus Infection in Nonpregnant Individuals -Assessment for Zika Virus Infection in Pregnant Women Zika virus testing is not recommended for asymptomatic couples attempting conception, given the potential for false-positive and false-negative results. Additionally, it is well established the Zika virus may remain in reproductive fluids, despite negative serologic and molecular test results in blood and urine.

**Useful For:** Screening for the presence of IgM-class antibodies to Zika virus in symptomatic pregnant women with either travel to a Zika virus endemic region or who have had sexual exposure to an individual with Zika virus

**Interpretation:** See the Zika virus algorithms in Special Instructions for a review of the recommended testing and interpretation of results. For the most recent CDC guidelines for Zika virus testing visit www.cdc.gov/zika/. Presumptive Zika Positive: IgM-class antibodies to Zika virus (ZIKV) detected. This is a preliminary result and does not confirm evidence of ZIKV infection. Definitive healthcare decisions should not be made based on this result alone. False-positive results may occur in patients with other current or prior flavivirus infections (eg, dengue virus). This specimen has been referred for confirmatory plaque reduction neutralization testing (PRNT) to the CDC or a CDC-designated laboratory. For patients with less than 14 days of symptoms or last possible exposure to ZIKV, real time (RT)-PCR for ZIKV on serum and urine is recommended. A positive ZIKV RT-PCR result on either specimen is confirmatory for ZIKV infection. Other Flavivirus Positive: Antibodies to a flavivirus, not Zika virus, were detected. Consider targeted testing for IgM-class antibodies to dengue and/or West Nile viruses as appropriate, taking into consideration patient exposure and presentation. Negative: No evidence of IgM-class antibodies to Zika virus (ZIKV). For specimens collected less than 14 days postsymptom onset or possible ZIKV exposure, the CDC recommends RT-PCR for ZIKV on serum and urine to exclude a false-negative ZIKV IgM result.

**Reference Values:**

**Negative**


**Previous Hepatitis (Unknown Type)**

**Clinical Information:** Hepatitis A: Hepatitis A virus (HAV) is an RNA virus that accounts for 20% to 25% of the viral hepatitis in United States adults. HAV infection is spread by the oral/fecal route and produces acute hepatitis that follows a benign, self-limited course. Spread of the disease is usually associated with contaminated food or water caused by poor sanitary conditions. Outbreaks frequently occur in overcrowded situations and in institutions or high density centers such as prisons and health care centers. Epidemics may occur following floods or other disaster situations. Chronic carriers of HAV have never been observed. Hepatitis B: Hepatitis B virus (HBV) is a DNA virus that is endemic throughout the world. The infection is spread primarily through percutaneous contact with infected blood products (eg, blood transfusion, sharing of needles by drug addicts). The virus is also found in virtually every type of human body fluid and is known to be spread through oral and genital contact. HBV can be transmitted
from mother to child during delivery through contact with blood and vaginal secretions; it is not commonly transmitted transplacentally. After a course of acute illness, HBV persists in approximately 10% of patients. Some of these chronic carriers are asymptomatic, others develop chronic liver disease, including cirrhosis and hepatocellular carcinoma. Hepatitis C: Hepatitis C virus (HCV) is an RNA virus that is a significant cause of morbidity and mortality worldwide. HCV is transmitted through contaminated blood or blood products or through other close, personal contacts. It is recognized as the cause of most cases of posttransfusion hepatitis. HCV shows a high rate of progression (>50%) to chronic disease. In the United States, HCV infection is quite common, with an estimated 3.5 to 4 million chronic HCV carriers. Cirrhosis and hepatocellular carcinoma are sequelae of chronic HCV. The following algorithms are available in Special Instructions: -HBV Infection-Diagnostic Approach and Management Algorithm -Hepatitis C: Testing Algorithm for Screening and Diagnosis -Viral Hepatitis Serologic Profiles

**Useful For:** Determining if an individual has been infected following exposure to an unknown type of hepatitis Obtaining baseline serologic markers of an individual exposed to a source with an unknown type of hepatitis Determining immunity to hepatitis A and B viral infections

**Interpretation:**

- **Hepatitis A:** Antibody against hepatitis A antigen (anti-HAV) is almost always detectable by the onset of symptoms (usually 15-45 days after exposure). The initial antibody consists almost entirely of the IgM subclass of antibody. Anti-HAV IgM usually falls to undetectable levels 3 to 6 months after infection. Anti-HAV IgG levels rise quickly once the virus is cleared and persist for many years. Hepatitis B: Hepatitis B surface antigen (HBsAg) is the first serologic marker appearing in the serum 6 to 16 weeks following hepatitis B virus (HBV) infection. In acute cases, HBsAg usually disappears 1 to 2 months after the onset of symptoms. Hepatitis B surface antibody (anti-HBs) appears with the resolution of HBV infection after the disappearance of HBsAg. Anti-HBs also appears as the immune response following a course of inoculation with the hepatitis B vaccine. Hepatitis B core antibody (anti-HBc) appears shortly after the onset of symptoms of HBV infection and may be the only serologic marker remaining years after exposure to hepatitis B. Hepatitis C: Hepatitis C virus antibody (anti-HCV) is usually not detectable during the early months following infection, but is almost always detectable by the late convalescent stage of infection. Anti-HCV is not neutralizing and does not provide immunity.

**Reference Values:**

- **HEPATITIS B SURFACE ANTIGEN**
  - Negative

- **HEPATITIS B SURFACE ANTIGEN CONFIRMATION**
  - Negative

- **HEPATITIS B SURFACE ANTIBODY, QUALITATIVE/QUANTITATIVE**
  - Hepatitis B Surface Antibody
    - Unvaccinated: negative
    - Vaccinated: positive

  - Hepatitis B Surface Antibody, Quantitative
    - Unvaccinated: <5.0 mIU/mL
    - Vaccinated: ≥12.0 mIU/mL

- **HEPATITIS B CORE TOTAL ANTIBODIES**
  - Negative

- **HEPATITIS A IgG ANTIBODY**
  - Unvaccinated: Negative
  - Vaccinated: Positive

- **HEPATITIS C ANTIBODY**
  - Negative

- **HEPATITIS C VIRUS RNA DETECTION and QUANTIFICATION by REAL-TIME RT-PCR**
Interpretation depends on clinical setting. See Viral Hepatitis Serologic Profiles in Special Instructions.


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### Primidone and Phenobarbital, Serum

**Clinical Information:** Primidone is used for control of grand mal seizures that are refractory to other antiepileptics and seizures of psychomotor or focal origin. Primidone is initially dosed in progressively increasing amounts starting with 100 mg at bedtime to 250 mg 3 times a day after 10 days of therapy in adults. Primidone exhibits a volume of distribution of 0.6 L/kg and a half-life of 8 hours. When monitoring primidone and phenobarbital levels simultaneously, the specimen should be drawn just before the next dose is administered. Primidone is not highly protein bound, approximately 10%. Phenobarbital is a metabolite of primidone. Like phenobarbital, there are no known major drug-drug interactions that affect the pharmacology of primidone. Toxicity associated with primidone is primarily due to the accumulation of phenobarbital. Diagnosis and treatment are as described for **PBAR / Phenobarbital, Serum.**

**Useful For:** Assessing compliance Monitoring for appropriate therapeutic levels of primidone and phenobarbital Assessing toxicity

**Interpretation:** At steady-state, which is achieved approximately 2 weeks after therapy is initiated, blood levels of primidone that correlate with optimal response to the drug range from 9.0 to 12.5 mcg/mL for adults and 7.0 to 10.0 mcg/mL for children <5 years of age. The corresponding levels for phenobarbital are 20.0 to 40.0 mcg/mL for adults and 15.0 to 30.0 mcg/mL for children <5 years of age. Dosage adjustment based on blood level information is the best way to obtain optimal response to the drug.

**Reference Values:**

**Primidone**
- Therapeutic: 5.0-12.0 mcg/mL
- Critical value: > or =15.0 mcg/mL

**Phenobarbital**
- Therapeutic: 10.0-40.0 mcg/mL
- Critical value: > or =60.0 mcg/mL


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### Privet Tree, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and
clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Procnainamide and N-acetylprocnainamide, Serum

Clinical Information: Procainamide (PA) is indicated in the treatment of premature ventricular contractions, ventricular tachycardia, atrial fibrillation, and paroxysmal atrial tachycardia. PA is contraindicated in patients with complete atrioventricular block. PA is metabolized to an active metabolite, N-acetylprocainamide (NAPA), with metabolism controlled by genetically determined enzymes. In patients with normal renal function, fast metabolizers will have a PA:NAPA ratio <1 at 3 hours after the dose is administered. Slow acetylators (PA:NAPA ratio >2 after 3 hours) are more likely to develop a positive test for antinuclear antibodies and present with systemic lupus erythematosus-like symptoms. Patients who have prolonged exposure to procainamide >12 mcg/mL or NAPA concentration > or = 40.0 mcg/mL are very likely to exhibit symptoms of toxicity that are characterized by hypotension, ventricular fibrillation, widened QRS complex, junctional tachycardia, oliguria, confusion, nausea, and vomiting. Renal disease, hepatic disease, cardiac failure, and states of low cardiac output reduce the metabolism and clearance of PA and NAPA. Co-administration of histamine H2 receptor antagonists, such as cimetidine and ranitidine reduce renal clearance of PA and NAPA resulting in higher plasma concentrations of each.

Useful For: Monitoring therapy with procainamide Assessing compliance Evaluating toxicity

Interpretation: Administration of a dose of 50 mg/kg will usually yield the optimal trough concentration in the range of 4.0 to 10.0 mcg/mL for procainamide and 12.0 to 18.0 mcg/mL for N-acetylprocainamide.
**Reference Values:**

**Procainamide**
- Therapeutic: 4.0-10.0 mcg/mL
- Critical value: >12.0 mcg/mL

**N-acetylprocainamide**
- Therapeutic: 12.0-18.0 mcg/mL
- Critical value: > or =40.0 mcg/mL

**Clinical References:** Myerburg RJ, Kessler KM, Kiem I, et al: Relationship between plasma levels of procainamide, suppression of premature ventricular complexes and prevention of recurrent ventricular tachycardia. Circulation 1981;64;280-290

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**Procalcitonin, Serum**

**Clinical Information:** Procalcitonin (ProCT) is a 116 amino acid precursor of calcitonin (CT). ProCT is processed to an N-terminal 57 amino acid peptide (CT [32 amino acids] and a 21 amino acid C-terminal peptide, catacalcin [CCP-1]). Expression of this group of peptides is normally limited to thyroid C cells and, to a small extent, other neuroendocrine cells. CT is the only hormonally active of these peptides. CT is secreted by C cells in response to hypercalcemia and inhibits bone resorption by osteoclasts, minimizing oscillations in serum calcium and calcium loss. During severe systemic inflammation, in particular related to bacterial infection, the tissue specific control of CT-related peptides expression breaks down and ProCT and CCP-1 (referred collectively to as ProCT) are secreted in large quantities by many tissues. CT levels do not change. Noninfectious inflammatory stimuli need to be extremely severe to result in ProCT elevations, making it a more specific marker for severe infections than most other inflammatory markers (cytokines, interleukins, and acute-phase reactants). ProCT elevations are also more sustained than those of most other markers and occur in neutropenic patients. This reduces the risk of false-negative results. ProCT becomes detectable within 2 to 4 hours after a triggering event and peaks by 12 to 24 hours. ProCT secretion parallels closely the severity of the inflammatory insult, with higher levels associated with more severe disease and declining levels with resolution of illness. In the absence of an ongoing stimulus, ProCT is eliminated with a half-life of 24 to 35 hours, making it suitable for serial monitoring. Finally, the dependence of sustained ProCT elevations on ongoing inflammatory stimuli allows identification of secondary septic events in conditions that can result in noninfectious ProCT elevations, such as cardiac surgery, severe trauma, severe burns, and multiorgan failure. ProCT levels should fall at a predictable pace in the absence of secondary infection.

**Useful For:** Diagnosis of bacteremia and septicemia in adults and children (including neonates)
- Diagnosis of renal involvement in urinary tract infection in children
- Diagnosis of bacterial infection in neutropenic patients
- Diagnosis, risk stratification, and monitoring of septic shock
- Diagnosis of systemic secondary infection post-surgery, and in severe trauma, burns, and multiorgan failure
- Differential diagnosis of bacterial versus viral meningitis
- Differential diagnosis of community-acquired bacterial versus viral pneumonia
- Monitoring of therapeutic response to antibacterial therapy

**Interpretation:** General considerations:
- In children older than 72 hours and in adults, levels <0.15 ng/mL make a diagnosis of significant bacterial infection unlikely. -Procalcitonin (ProCT) between 0.15 and 2.0 ng/mL do not exclude an infection, because localized infections (without systemic signs) may be associated with such low levels. -Levels >2.0 ng/mL are highly suggestive of systemic bacterial infection/sepsis or severe localized bacterial infection, such as severe pneumonia, meningitis, or peritonitis. They can also occur after severe noninfectious inflammatory stimuli such as major burns, severe trauma, acute multiorgan failure, or major abdominal or cardiothoracic surgery. In cases of noninfectious elevations, ProCT levels should begin to fall after 24 to 48 hours. -Autoimmune diseases, chronic inflammatory processes, viral infections, and mild localized bacterial infections rarely lead to elevations of ProCT of >0.5 ng/mL. Specific diagnostic applications, based on the current consensus in the literature:
- Diagnosis of bacteremia in neonates: After birth ProCT values increase from birth to reach peak values at about 24 hours of life and the decrease gradually by 48 hours of life. Therefore, during the first 72 hours of life different reference ranges will apply to newborn infants at different hours of age. ProCT levels on newborns suffering from early sepsis are significantly higher than those of noninfected...
newborns when reference ranges by hours of age are used.(1,2) Adult levels should apply at > or =72 hours after birth. - Diagnosis of renal involvement in pediatric urinary tract infections: In children with urinary tract infections, a ProCT level of >0.5 ng/mL has a 70% to 90% sensitivity and an 80% to 90% specificity for renal involvement. - ProCT responses in neutropenic patients are similar to patients with normal neutrophil counts and function, and the cutoffs discussed under general considerations above should be used. In the appropriate clinical setting, ProCT levels above 2.0 ng/mL on the first day of admission to the intensive care unit (ICU) represent a high risk for progression to severe sepsis and/or septic shock. ProCT levels below 0.5 ng/mL on the first day of ICU admission represent a low risk for progression to severe sepsis and/or septic shock. Reported sensitivity and specificity for the diagnosis of sepsis range from 60% to 100%, depending on underlying and coexisting diseases and the patient populations studied. The higher the ProCT level the worse the prognosis. A ProCT level of <0.5 ng/mL makes bacterial meningitis very unlikely. Most patients with bacterial meningitis will have ProCT levels of >10 times this level. With successful antibiotic therapy, ProCT levels should fall with a half-life to 24 to 35 hours.

Reference Values:
Adults and children > or =72 hours: < or =0.15 ng/mL
Children < 72 hours: <2.0 ng/mL at birth, rises to < or =20 ng/mL at 18-30 hours of age, then falls to < or =0.15 ng/mL by 72 hours of age


Procollagen I Intact N-Terminal, Serum
Clinical Information: Procollagen type I propeptides are derived from collagen type I, which is the most common collagen type found in mineralized bone. In bone, collagen is synthesized by osteoblasts in the form of procollagen. This precursor contains a short signal sequence and terminal extension peptides: amino-terminal propeptide (PINP) and carboxy-terminal propeptide. These propeptide extensions are removed by specific proteinases before the collagen molecules form. Both propeptides can be found in the circulation and their concentration reflects the synthesis rate of collagen type I. Although collagen type I propeptides may also arise from other tissues (such as the skin, vessels, fibrocartilage, and tendons), most nonskeletal tissues exhibit a slower turnover than bone, and contribute very little to the circulating pool of PINP. PINP is considered the most sensitive marker of bone formation and it is particularly useful for monitoring bone formation therapies and antiresorptive therapies; it is recommended that the test be performed at baseline before starting osteoporosis therapy and again 3 to 6 months later. PINP could be detected in the circulation as the "intact" or trimeric molecule and the monomer. In osteoporosis subjects with normal renal function, the predominant form of PINP detected in circulation is the trimeric form. However, monomeric PINP fragments may accumulate in patients with renal failure or metastatic bone disease.

Useful For: An aid in monitoring antiresorptive and anabolic therapy in patients with osteoporosis
An adjunct in the assessment of conditions associated with increased bone turnover such as Paget disease

Interpretation: This test should be performed before beginning osteoporosis treatment (ie, prior to the start of therapy) to establish a baseline procollagen I intact N-terminal (PINP) level. Three to 6
months after initiation of therapy, a change of > or =21% (least significant change) from baseline PINP levels indicates an adequate therapeutic response. This assay is specific for the intact trimeric form of PINP. The direction of the change in PINP levels (decrease or increase) will depend on the type of osteoporosis treatment. In patients taking bisphosphonates, PINP levels have been shown to decrease up to 70% from baseline after 6 months of therapy. Treatment with hormone replacement therapy also shows a decrease in PINP levels, but to a lesser degree than bisphosphonates therapy. In patients treated with teriparatide (recombinant human parathyroid hormone 1-34), PINP levels increase from baseline reflecting the stimulatory effect of teriparatide on osteoblasts and bone formation. PINP levels have been shown to significantly increase as early as 1 month after teriparatide treatment, peaking at 6 months following treatment. Increases of >10 mcg/L have been reported in 77% to 79% of teriparatide-treated patients after 3 months of therapy and are considered a successful response.

Reference Values:
Reference values have not been established for patients who are <18 years of age.
Adult male: 22-87 mcg/L
Adult female premenopausal: 19-83 mcg/L
Adult female postmenopausal: 16-96 mcg/L

**Paraffin-Embedded Tissue**

**Clinical Information:** Products of conception (POC) are tissues created at conception that spontaneously miscarry; these tissues include choriocarcinoid villi, fetal membranes, or fetal tissue. Spontaneous miscarriages occur in 15% to 20% of all recognized human conceptions. While there are many possible causes for miscarriages, chromosome anomalies can be identified in up to 50% of first-trimester miscarriages. It is important to determine a possible chromosomal cause of the pregnancy loss as this information impacts patient management and facilitates understanding of the reason for the loss. Chromosomal aneuploidy, the gain or loss of chromosomes, is a major cause of early fetal demise. Trisomy is the most common type of chromosome abnormality in spontaneous abortions and has been observed for most chromosomes, with 13, 15, 16, 18, 21, 22, X, and Y being the most common. Chromosomal microarray analysis of POC (CMAMT / Chromosomal Microarray, POC, FFPE) is available when a more comprehensive assessment for chromosome abnormalities is desired.

**Useful For:** Screening for chromosomal aneuploidies of chromosomes 13, 15, 16, 18, 21, 22, X, and Y when fresh tissue is not available

**Interpretation:** Aneuploidy is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:** Laurino MY, Bennett RL, Saraiya DS, et al: Genetic evaluation and counseling of couples with recurrent miscarriage: recommendations of the National Society of Genetic Counselors. J Genet Couns 2005;14:165-181

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**Progesterone Receptor (PR) Immunostain, Technical Component Only**

**Clinical Information:** Progesterone receptor is a hormone receptor localized within the nucleus. It is highly expressed in the epithelial cells of the breast and endometrium, and smooth muscle cells of the uterus. This antibody is used along with that for estrogen receptor to assess hormonal responsiveness in breast cancer.

**Useful For:** Qualitative detection of progesterone receptor protein in a diagnostic setting

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**Progesterone, Serum**

**Clinical Information:** Sources of progesterone are the adrenal glands, corpus luteum, and placenta. Adrenal Glands: Progesterone synthesized in the adrenal glands is converted to other corticosteroids and androgens and, thus, is not a major contributor to circulating serum levels unless there is a progesterone-producing tumor present. Corpus Luteum: After ovulation, there is a significant rise in
serum levels as the corpus luteum begins to produce progesterone in increasing amounts. This causes changes in the uterus, preparing it for implantation of a fertilized egg. If implantation occurs, the trophoblast begins to secrete human chorionic gonadotropin, which maintains the corpus luteum and its secretion of progesterone. If there is no implantation, the corpus luteum degenerates and circulating progesterone levels decrease rapidly, reaching follicular phase levels about 4 days before the next menstrual period. Placenta: By the end of the first trimester, the placenta becomes the primary secretor of progesterone.

**Useful For:** Ascertaining whether ovulation occurred in a menstrual cycle Assessment of infertility Evaluation of abnormal uterine bleeding Evaluation of placental health in high-risk pregnancy Determining the effectiveness of progesterone injections when administered to women to help support early pregnancy Workup of some patients with adrenal disorders

**Interpretation:** Ovulation results in a midcycle surge of luteinizing hormone (LH) followed by an increase in progesterone secretion, peaking between day 21 and 23. If no fertilization and implantation has occurred by then, supplying the corpus luteum with human chorionic gonadotropin-driven growth stimulus, progesterone secretion falls, ultimately triggering menstruation. Typically, day 21 to 23 serum progesterone concentrations of more than 10 ng/mL indicate normal ovulation and concentrations below 10 ng/mL suggest anovulation, inadequate luteal phase progesterone production, or inappropriate timing of sample collection. Increased progesterone concentrations are occasionally seen with some ovarian cysts, molar pregnancies, rare forms of ovarian cancer, adrenal cancer, congenital adrenal hyperplasia, and testicular tumors. Increased progesterone may also be a result of overproduction by the adrenal glands. Low concentrations of progesterone may be associated with toxemia in late pregnancy, decreased ovarian function, amenorrhea, ectopic pregnancy, and miscarriage.

**Reference Values:**

**Males:**
- <4 weeks: Not established
- 4 weeks-<12 months: < or =0.66 ng/mL (confidence interval 0.63-0.94 ng/mL)
- 12 months-9 years: < or =0.35 ng/mL
- 10-17 years:
  - Concentrations increase through adolescence and puberty
  - 12 months-9 years: < or =0.35 ng/mL
  - > or =18 years (central 90th %): <0.20 ng/mL
- > or =18 year:
  - Concentrations increase through adolescence and puberty
  - 12 months-9 years: < or =0.35 ng/mL
  - Adult (central 90th %):
    - Follicular phase: < or =0.89 ng/mL
    - Ovulation: < or =12 ng/mL
    - Luteal phase: 1.8-24 ng/mL
    - Pregnancy
      - 1st trimester: 11-44 ng/mL
      - 2nd trimester: 25-83 ng/mL
      - 3rd trimester: 58-214 ng/mL
- > or =18 years:
  - Concentrations increase through adolescence and puberty
  - Follicular phase: < or =0.89 ng/mL
  - Ovulation: < or =12 ng/mL
  - Luteal phase: 1.8-24 ng/mL
  - Post-menopausal: < or =0.20 ng/mL
  - Pregnancy

**Females:**
- <4 days old: Not established
- 4 days-<12 months: < or =1.3 ng/mL (confidence interval 0.88-2.3 ng/mL)
- 12 months-9 years: < or =0.35 ng/mL
- 10-17 years:
  - Adult concentrations are attained by puberty
  - 12 months-9 years: < or =0.35 ng/mL
  - Adult (central 90th %):
    - Follicular phase: < or =0.89 ng/mL
    - Ovulation: < or =12 ng/mL
    - Luteal phase: 1.8-24 ng/mL
    - Pregnancy
      - 1st trimester: 11-44 ng/mL
      - 2nd trimester: 25-83 ng/mL
      - 3rd trimester: 58-214 ng/mL
  - > or =18 years:
    - Concentrations increase through adolescence and puberty
    - Follicular phase: < or =0.89 ng/mL
    - Ovulation: < or =12 ng/mL
    - Luteal phase: 1.8-24 ng/mL
    - Post-menopausal: < or =0.20 ng/mL
    - Pregnancy

Current as of October 11, 2018 2:20 pm CDT   800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com   Page 1882
- 1st trimester: 11-44 ng/mL
- 2nd trimester: 25-83 ng/mL
- 3rd trimester: 58-214 ng/mL


For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.

**Clinical References:**

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**Programmed Death-Ligand 1 (PD-L1) (22C3), Semi-Quantitative Immunohistochemistry, Manual**

**Clinical Information:** Programmed cell death 1-ligand 1 (PD-L1), also known as B7 homolog 1 (B7-H1) or CD274, is a transmembrane protein involved in the regulation of cell-mediated immune responses through interaction with the receptor programmed death protein-1 (PD-1). PD-L1 has been identified as both a prognostic and theranostic marker in a variety of neoplasms. Overexpression of PD-L1 has been observed in carcinomas of the urinary bladder, lung, gastric and gastroesophageal junction, thymus, colon, pancreas, ovary, breast, kidney, and in melanoma and glioblastoma.

**Useful For:** Identification of neoplasms expressing programmed cell death 1-ligand 1 (clone 22C3)

**Interpretation:** This test will be reported as percent tumor cells positive and whether greater than or equal to 5% of immune cells express programmed cell death 1-ligand 1 (PD-L1) or not. For gastric and gastroesophageal junctional adenocarcinoma, PD-L1 will be reported as combined positive score (CPS). If additional interpretation or analysis is needed, request PATHC / Pathology Consultation along with this test.

**Clinical References:**

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**Programmed Death-Ligand 1 (PD-L1) (SP142), Semi-Quantitative Immunohistochemistry, Manual**

**Clinical Information:** Programmed cell death 1-ligand 1 (PD-L1), also known as B7 homolog 1 (B7-H1) or CD274, is a transmembrane protein involved in the regulation of cell-mediated immune responses through interaction with the receptor programmed death protein-1 (PD-1). PD-L1 has been identified as both a prognostic and theranostic marker in a variety of neoplasms. Overexpression of PD-L1 has been observed in carcinomas of the urinary bladder, lung, thymus, colon, pancreas, ovary, breast, kidney, and in melanoma and glioblastoma.
**Useful For:** Identification of neoplasms expressing programmed cell death 1-ligand 1 (clone SP142)

**Interpretation:** This test will be answered as percent tumor cells positive and whether greater than or equal to 5% of immune cells express PD-L1 or not. If additional interpretation or analysis is needed, request test PATHC / Pathology Consultation along with this test.

**Clinical References:**

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**Programmed Death-Ligand 1 (PD-L1) (SP263), Semi-Quantitative Immunohistochemistry, Manual**

**Clinical Information:** Programmed cell death 1-ligand 1 (PD-L1), also known as B7 homolog 1 (B7-H1) or CD274, is a transmembrane protein involved in the regulation of cell-mediated immune responses through interaction with the receptor programmed death protein-1 (PD-1). PD-L1 has been identified as both a prognostic and theranostic marker in a variety of neoplasms. Overexpression of PD-L1 has been observed in carcinomas of the urinary bladder, lung, thymus, colon, pancreas, ovary, breast, kidney, and in melanoma and glioblastoma.

**Useful For:** Identification of neoplasms expressing programmed cell death 1-ligand 1 (clone SP263)

**Interpretation:** This test will be answered as percent tumor cells positive and whether greater than or equal to 5% of immune cells express PD-L1 or not. If additional interpretation or analysis is needed, request test PATHC / Pathology Consultation along with this test.

**Clinical References:**

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**Progranulin Gene (GRN), Full Gene Analysis**

**Clinical Information:** Frontotemporal lobar degeneration (FTLD) describes a group of neurodegenerative diseases that are frequent causes of dementia, accounting for 5% to 10% of all dementia patients and 10% to 20% of patients with onset of dementia before age 65. Frontotemporal dementia (FTD) is the most common clinical manifestation of FTLD. The clinical presentation of FTD is variable, but typically includes changes in personality and social conduct, often associated with impulse disinhibition, followed by more general cognitive decline, eventually leading to dementia. The age of onset is extremely variable ranging from 35 to 87 years. Duration of the disease ranges from 3 to 12 years. Based on the immunohistochemical staining, there are 2 main subtypes of FTLD: tau-positive FTLD and tau-negative FTLD with ubiquitin-positive inclusions (FTLD-U). Mutations in the MAPT gene have been identified in patients with tau-positive FTLD; mutations in the progranulin gene (GRN) have been
identified in patients with FTLD-U. Both MAPT and GRN are located on chromosome 17q21, with GRN located only 1.7 Mb centromeric of MAPT. GRN consists of 12 coding and 1 noncoding exons. GRN encodes progranulin, a multifunctional protein that plays a role in multiple processes including development, wound repair, and inflammation. The function of GRN in the brain is not well understood, but progranulin is widely expressed in neurons and glial cells. More than 40 different pathogenic GRN mutations have been reported. All pathogenic mutations identified to date create functional null alleles that result in decreased progranulin production, suggesting that reduced levels of progranulin may lead to neurodegeneration.

**Useful For:** Aiding the diagnosis of frontotemporal dementia Distinguishing frontotemporal dementia from other dementias, including Alzheimer dementia Identifying individuals who are at increased risk of frontotemporal dementia

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.

**Clinical References:**

**Proinsulin, Plasma**

**Clinical Information:** Proinsulin is the precursor of insulin and C-peptide. Following synthesis, proinsulin is packaged into secretory granules, where it is processed to C-peptide and insulin by prohormone convertases (PC1/3 and PC2) and carboxypeptidase E. Only 1% to 3% of proinsulin is secreted intact. However, because proinsulin has a longer half-life than insulin, circulating proinsulin concentrations are in the range of 5% to 30% of circulating insulin concentrations on a molar basis, with the higher relative proportions seen after meals and in patients with insulin resistance or early type 2 diabetes. Proinsulin can bind to the insulin receptor and exhibits 5% to 10% of the metabolic activity of insulin. Proinsulin levels might be elevated in patients with insulin-producing islet cell tumors (insulinomas). These patients suffer from hypoglycemic attacks due to inappropriate secretion of insulin by the tumors. The biochemical diagnosis rests primarily on demonstrating non-suppressed insulin levels in the presence of hypoglycemia (blood glucose <45 mg/dL). The diagnosis can be difficult, as tumors might be small or secrete insulin only episodically. Insulin injections or hypoglycemic drugs can also mimic insulinoma. Evaluation of these patients frequently requires a prolonged fast (72 hours), as well as supplementary tests in addition to insulin and glucose measurements, including a sulfonylurea screen, and measurement of c-peptide, proinsulin, and beta-hydroxybutyrate. The inappropriate oversecretion of insulin by insulinomas causes the release of an increased numbers of secretory granules with incompletely processed insulin, resulting in elevated serum/plasma proinsulin concentrations. This oversecretion of proinsulin in insulinomas is accentuated during fasting, when proinsulin normally does not account for more than 5% of the insulin concentrations. Proinsulin is strikingly elevated in PC1/3 deficiency. These patients have defects in the processing of multiple peptide hormones and suffer from diabetes, adrenal insufficiency, infertility, and obesity. Affected individuals typically have red hair regardless of racial background. Mutations in the proinsulin molecule have been reported that affect PC cleavage efficiency or subsequent proinsulin metabolism. These mutations can also lead to markedly elevated proinsulin levels, but are usually not accompanied by diabetes, or any other hormonal abnormalities.
Useful For: As part of the diagnostic workup of suspected insulinoma As part of the diagnostic workup of patients with suspected prohormone convertases1/3 deficiency As part of the diagnostic workup of patients with suspected proinsulin mutations

Interpretation: Normal individuals will have proinsulin concentrations below the upper limit of the normal fasting reference range (22 pmol/L) when hypoglycemic (blood glucose <60 mg/dL). Conversely, most (>80%) insulinoma patients will have proinsulin concentrations above the upper limit of the reference range. The sensitivity and specificity for a diagnosis of insulinoma during hypoglycemia are approximately 75% and near 100%, respectively, at the 22 pmol/L cutoff. A higher sensitivity (>95%) can be achieved using a 5 pmol/L cutoff, and this is the cutoff recommended by Mayo Clinic's highly experienced hypoglycemia team to avoid missing cases. However, the lower cutoff results in a reduced specificity (approximately 40%), emphasizing the need for a combination of different tests to assure accurate biochemical diagnosis. Patients with PC1/3 deficiency have low, or sometimes undetectable, insulin levels and substantially elevated proinsulin levels, exceeding the upper limit of the reference range substantially in the fasting state and rising even higher after food intake. Many other hormonal abnormalities are also present, including cortisol deficiency (because of lack of processing of pro-opiomelanocortin to adrenocorticotropic hormone and other peptides), infertility, and, often, obesity.

Reference Values: 3.6-22 pmol/L


PRLI

Clinical Information: Prolactin is a pituitary hormone involved in the stimulation of milk production, salt and water regulation, growth, development, and reproduction. Prolactin-producing cells constitute approximately 20% of the cells of the normal anterior pituitary. Antibodies to prolactin are used in a panel to subclassify pituitary adenomas.

Useful For: Subclassification of pituitary adenomas

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Prolactin, Pituitary Macroadenoma, Serum

Clinical Information: Prolactin-secreting macroadenomas (>10 mm in diameter) can sometimes produce exceedingly high serum prolactin concentrations that may paradoxically result in falsely low prolactin concentrations when measured by immunometric assays. In such situations, very high concentrations of prolactin saturate both the capture and signal antibodies in the assay, block formation of the capture antibody-prolactin-signal antibody “sandwich,” and result in falsely decreased prolactin results (referred to as the high-dose hook effect). With such tumors, serum prolactin levels may be falsely decreased into the normal reference interval, potentially resulting in inappropriate patient management. Dilution of the specimen eliminates the analytic artifact in these cases. Prolactin is secreted by the anterior pituitary gland and controlled by the hypothalamus. The major chemical controlling prolactin secretion is dopamine, which inhibits prolactin secretion from the pituitary. Prolactin is released from the pituitary in response to thyrotropin-releasing hormone and other factors. Prolactin is the principal hormone that controls the initiation and maintenance of lactation. In normal individuals, prolactin concentrations increase in response to physiologic stimuli such as sleep, stress, exercise, sexual intercourse, and hypoglycemia, and are also elevated during pregnancy, lactation, postpartum, and in the newborn infant. Hyperprolactinemia is the most common hypothalamic-pituitary disorder encountered in clinical endocrinology. Pathologic causes of hyperprolactinemia include prolactin-secreting pituitary adenoma (prolactinoma, which is more frequent in females than males, and accounts for approximately 40% of all pituitary tumors), functional and organic disease of the hypothalamus, primary hypothyroidism, compression of the pituitary stalk, chest wall lesions, renal insufficiency, polycystic ovarian disease, and ectopic tumors. In general, serum prolactin concentrations parallel tumor size in patients with prolactinomas. Macroadenomas (>10 mm in diameter) are typically associated with serum prolactin concentrations >250 ng/mL and a concentration >500 ng/mL is diagnostic of a macroadenoma. Moderately increased concentrations of serum prolactin are not a reliable guide for determining whether a prolactin-producing pituitary adenoma is present. Multiple medications can cause increased prolactin concentration including estrogens, dopamine receptor blockers (eg, phenothiazines), dopamine antagonists (eg, metoclopramide, domperidone), alpha-methyldopa, cimetidine, opiates, antihypertensive medications, and other antidepressants and antipsychotics. Hyperprolactinemia often results in loss of libido, galactorrhea, oligomenorrhea or amenorrhea, and infertility in premenopausal females; and loss of libido, impotence, infertility, and hypogonadism in males. Postmenopausal and premenopausal women, as well as men, can also suffer from decreased muscle mass and osteoporosis. Prolactinomas may rarely present in childhood or adolescence. In girls, disturbances in menstrual function and galactorrhea may be seen, whereas in boys, delayed pubertal development and hypogonadism are often present. The treatment options are the same as in adult patients.

Useful For: Quantifying prolactin in serum specimens where the high-dose hook effect is suspected (eg, presence of pituitary tumor with symptoms of prolactinoma, and lower than expected serum prolactin concentration)

Interpretation: If no high-dose hook effect is observed, the following report comment will be included with the prolactin result: 10-, 100-, and 400-fold dilutions produced results consistent with the absence of high-dose hook effect. Total prolactin was measured using the Roche Cobas e immunoassay analyzer. If a high-dose hook effect is observed, which is demonstrated by significantly increasing concentrations of prolactin obtained after dilution of the serum, an interpretive comment will be included with the prolactin result. The Roche Cobas Prolactin II assay should demonstrate no high-dose hook effect at prolactin concentrations up to approximately 12,500 ng/mL (see Method Description).

Reference Values:

Males
<18 years: not established
> or = 18 years: 4.0-15.2 ng/mL

Females:
<18 years: not established
> or = 18 years: 4.8-23.3 ng/mL

PRL 85670

Prolactin, Serum

Clinical Information: Prolactin is secreted by the anterior pituitary gland and controlled by the hypothalamus. The major chemical controlling prolactin secretion is dopamine, which inhibits prolactin secretion from the pituitary. Prolactin is released from the pituitary in response to thyrotropin-releasing hormone and other factors. Prolactin is the principal hormone that controls the initiation and maintenance of lactation. In normal individuals, prolactin concentrations increase in response to physiologic stimuli such as sleep, stress, exercise, sexual intercourse, and hypoglycemia, and are also elevated during pregnancy, lactation, postpartum, and in the newborn infant. Hyperprolactinemia is the most common hypothalamic-pituitary disorder encountered in clinical endocrinology. Pathologic causes of hyperprolactinemia include prolactin-secreting pituitary adenoma (prolactinoma, which is more frequent in females than males and accounts for approximately 40% of all pituitary tumors), functional and organic disease of the hypothalamus, primary hypothyroidism, compression of the pituitary stalk, chest wall lesions, renal insufficiency, polycystic ovarian disease, and ectopic tumors. Hyperprolactinemia often results in loss of libido, galactorrhea, oligomenorrhea or amenorrhea, and infertility in premenopausal females, and loss of libido, impotence, infertility, and hypogonadism in males. Postmenopausal and premenopausal women, as well as men, can also suffer from decreased muscle mass and osteoporosis. Prolactinomas may rarely present in childhood or adolescence. In girls, disturbances in menstrual function and galactorrhea may be seen, whereas in boys, delayed pubertal development and hypogonadism are often present. The treatment options are the same as in adult patients.

Useful For: Aiding in evaluation of pituitary tumors, amenorrhea, galactorrhea, infertility, and hypogonadism Monitoring therapy of prolactin-producing tumors

Interpretation: In general, serum prolactin concentrations parallel tumor size in patients with prolactinomas. Macroadenomas (>10 mm in diameter) are typically associated with serum prolactin concentrations above 250 ng/mL, and a concentration above 500 ng/mL is diagnostic of a macroprolactinoma. Moderately increased concentrations of serum prolactin are not a reliable guide for determining whether a prolactin-producing pituitary adenoma is present. After initiation of medical therapy of prolactinomas, prolactin levels should decrease substantially in most patients; in 60% to 80% of patients, normal levels should be reached. Failure to suppress prolactin levels may indicate tumors resistant to the usual central-acting dopamine agonist therapies; however, a subset of patients will show tumor shrinkage despite persistent hyperprolactinemia. Patients who show neither a decrease in prolactin levels nor tumor shrinkage might require additional therapeutic measures. In patients where a discrepancy between pituitary tumor size and prolactin elevation is observed, a test for false-low serum prolactin (hook effect) should be performed by serial dilution. See PLPMA / Prolactin, Pituitary Macroadenoma. The Roche Cobas Prolactin II assay should demonstrate no high-dose hook effect at prolactin concentrations up to approximately 12,500 ng/mL. (Package insert: Roche E170/Cobas e601/e602 Prolactin II) Multiple medications can cause increased prolactin concentration including estrogens, dopamine receptor blockers (eg, phenothiazines), dopamine antagonists (eg, metoclopramide, domperidone), alpha-methylidopa, cimetidine, opiates, antihypertensive medications, and other antidepressants and antipsychotics. In patients with asymptomatic hyperprolactinemia, assessment for macroprolactin (prolactin bound to immunoglobulin) is suggested. Macroprolactin is detected by differing degrees depending on the immunoassay used to measure prolactin. The Roche Cobas Prolactin II assay shows low reactivity with most forms of macroprolactin. Macroprolactin should be evaluated in asymptomatic hyperprolactinemic subjects or when pituitary imaging studies are not informative. See MCRPL / Macroprolactin, Serum.
Reference Values:
Males
<18 years: not established
> or =18 years: 4.0-15.2 ng/mL

Females:
<18 years: not established
> or =18 years: 4.8-23.3 ng/mL

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.


Prolonged Clot Time Profile

Clinical Information: When coagulation screening tests are performed to verify normal function of the coagulation system (eg, preoperative, routine examination), they sometimes indicate an abnormality that may be unexplained (ie, prolonged clotting times). This consultation provides validation of the prolongation and as comprehensive a workup as needed to define the abnormality. Possibilities for a cause of prolongation include: -Factor deficiencies, congenital or acquired -Factor inhibitors (including Coumadin therapy) -Lupus-like anticoagulant -Heparin contamination -Dilution of specimen by anticoagulant if patient hematocrit is 55% or greater

Useful For: Determining the cause of prolongation of prothrombin time or activated partial thromboplastin time Screening for prolonged clotting times and determining the presence of factor deficiencies or inhibitor (eg, factor-specific, lupus-like, or the presence of heparin)

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.


Prolyl Hydroxylase Domain-2 (PHD2/EGLN1) Gene Sequencing

Clinical Information: Erythrocytosis (increased RBC mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (polycythemia vera: PV), or secondary, in response to increased erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other EPO-secreting tumors. When extrinsic causes of erythrocytosis are excluded, a heritable cause intrinsic to the RBC or erythrocyte regulatory mechanisms may be suspected. Mutations in genes coding for hemoglobin (high-oxygen-affinity hemoglobin variants), hemoglobin-stabilization proteins (2,3 bisphosphoglycerate deficiency), the erythropoietin receptor and oxygen-sensing pathway enzymes (hypoxia-inducible factor, prolyl hydroxylase domain, and von Hippel Lindau) can result in erythrocytosis (see Table). Erythrocytosis Testing Gene Inheritance Serum EPO p50 JAK2V617F Acquired Decreased Normal
The oxygen sensing pathway functions through an enzyme, hypoxia-inducible factor (HIF) that regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including EPO. HIF-alpha is regulated by von Hippel-Lindau (vHL) protein-mediated ubiquitination and proteosomal degradation, which requires prolyl hydroxylation of the serine and histidine residues. Enzymes important in the hydroxylation of HIF are the prolyl hydroxylase domain proteins, which have 3 isoforms-PHD1, PHD2, and PHD3. The most significant isoform associated with erythrocytosis is PHD2. PHD enzymes are oxygen dependent and have an iron-containing active site. Ascorbic acid enhances, but is not essential for, the activity of PHD. Therefore, activity can be modulated by low iron and ascorbic acid levels as well as by low oxygen. Clinically significant PHD2 (official designation EGLN1 [egl nine homolog 1]) mutations are heterozygous and have been found in exons 1 through 4. These mutations result in amino acid substitutions and are associated with inappropriately normal EPO levels.

**Useful For:** The definitive evaluation of an individual with JAK2-negative erythrocytosis associated with lifelong sustained increased RBC mass, elevated RBC count, hemoglobin, or hematocrit

**Interpretation:** An interpretive report will be provided as a part of the HEMP / Hereditary Erythrocytosis Mutations, and will include specimen information, assay information, and whether the specimen was positive for any mutations in the gene. If positive, the mutation will be correlated with clinical significance, if known.

**Reference Values:**
Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations.

**Clinical References:**

**FPHEG**  
90101  
**Promethazine (Phenergan)**  
Reference Values:  
Reference Range: < 150 ng/mL

**FIBDD**  
57459  
**PROMETHEUS IBD sgi Diagnostic**  
Reference Values:  
Testing is complete. Final report has been sent to the referring laboratory.

**FPLAC**  
91783  
**PROMETHEUS LactoTYPE**  
Reference Values:  
A final report will be attached in MayoAccess.

**FPMET**  
91564  
**Prometheus Thiopurine Metabolites**  
Reference Values:  
Units of Measure: pmol/8 x 10(8) RBC
Proprietary and patented technology by Prometheus Laboratories, Inc. The therapeutic range and toxic thresholds were established in an IBD patient population receiving azathioprine or 6-mercaptopurine. Metabolite testing should not replace laboratory monitoring for toxicity.


Propafenone, Serum

Clinical Information: Tocainide, mexiletine, flecainide, and propafenone are all class I antiarrhythmic agents whose dominant cardiac effect is to reduce the rate of rise of the action potential in cardiac cells. In so doing, they increase the threshold of excitability of myocardial cells, depress the conduction velocity of the impulse around the heart, and prolong the defective refractory period, which results in stabilization of the heart rate. All 4 drugs are effective following oral administration. Tocainide, mexiletine, and flecainide undergo minimal first-pass metabolism and have relatively long half-lives (10-16 hours). In contrast, propafenone undergoes extensive first-pass metabolism (half-life is approximately 1-3 hours). Its clinical efficacy is maintained through the formation of a metabolite (5-hydroxypropafenone) that is more pharmacologically active than the parent drug and has a longer plasma half-life (6-12 hours). Propafenone is primarily used to treat ventricular arrhythmias (ventricular tachycardia, supraventricular tachycardia, and ventricular premature contractions). Specimens should only be drawn after patient has been receiving propafenone orally for at least 3 days. Trough concentrations should be drawn just before administration of the next dose. Adverse side effects are seen in the central nervous system, skin, and gastrointestinal tract.

Useful For: Monitoring propafenone therapy

Interpretation: The therapeutic concentration is 0.5 to 2.0 mcg/mL; concentrations <0.5 mcg/mL likely indicate inadequate therapy and propafenone >2.0 mcg/mL indicates excessive therapy. Toxic concentration: >2.0 mcg/mL

Reference Values: Therapeutic concentration: 0.5-2.0 mcg/mL


Propofol, Serum/Plasma

Reference Values: Reporting limit determined each analysis
Patients required a mean blood propofol concentration of 4.05 +/- 1.01 mcg/mL for major surgery and 2.97 +/- 1.07 mcg/mL for non-major surgery. Blood propofol concentrations at which 50% of patients were awake and oriented after surgery were 1.07 and 0.95 mcg/mL respectively.

Psychomotor performance returned to baseline at blood propofol concentrations of 0.38 â€“ 0.43 mcg/mL.

**Prostaglandin D2 (PG D2), Urine**

**Clinical Information:** Prostaglandins are fatty acids derived from arachidonic acid metabolism. They are closely related to the Thromboxanes and Leukotrienes. Prostaglandin D2 is derived mainly from Prostaglandin H2, and is metabolized to Dihydroketo Prostaglandin D2. Prostaglandin D2 is excreted directly into the urine. The sites of highest Prostaglandin D2 activity are the brain, spinal cord, intestines, and stomach. Prostaglandin D2 is the major Prostaglandin produced by uterine tissue. Prostaglandin D2 is a potent bronchoconstrictor, neuromodulator, and anti-antithrombin agent. It also stimulates the secretion of Pancreatic Glucagon. Prostaglandin D2 has been found to have an anti-metastatic effect on many malignant tumor cells. Prostaglandin D2 production and circulating levels are drastically suppressed by aspirin and indomethacin.

**Reference Values:**
No reference intervals available for this test.

**Prostaglandin D2 (PGD2), Serum or Plasma**

**Clinical Information:** Prostaglandins are fatty acids derived from arachidonic acid metabolism. They are closely related to the Thromboxanes and Leukotrienes. Prostaglandin D2 is derived mainly from Prostaglandin H2, and is metabolized to Dihydroketo Prostaglandin D2. Prostaglandin D2 is excreted directly into the urine. The sites of highest Prostaglandin D2 activity are the brain, spinal cord, intestines, and stomach. Prostaglandin D2 is the major Prostaglandin produced by uterine tissue. Prostaglandin D2 is a potent bronchoconstrictor, neuromodulator, and anti-antithrombin agent. It also stimulates the secretion of Pancreatic Glucagon. Prostaglandin D2 has been found to have an anti-metastatic effect on many malignant tumor cells. Prostaglandin D2 production and circulating levels are drastically suppressed by aspirin and indomethacin.

**Reference Values:**
35 - 115 pg/mL

No pediatric reference ranges available for this test.

**Prostate Health Index (phi), Serum**

**Clinical Information:** Prostate-specific antigen (PSA) is a glycoprotein produced by the prostate gland, the lining of the urethra, and the bulbourethral gland. Normally, very little PSA is secreted in the blood. In conditions of increase glandular size and/or tissue damage, PSA is released into circulation. Measurement of serum PSA is useful for determining the extent of prostate cancer and assessing the response to prostate cancer treatment. PSA is also used as a screening tool for prostate cancer detection, although its use in screening has become controversial in recent years. While an elevated serum PSA is associated with prostate cancer, a number of benign conditions, such as benign prostatic hyperplasia (BPH) and prostatitis might lead to elevated serum PSA concentrations. As a consequence PSA lacks specificity for prostate cancer detection. Several PSA isoforms have been identified that can further increase the specificity of PSA for prostate cancer. In particular, the [-2] form of proPSA (p2PSA) shows improved performance over either total or free PSA for prostate cancer detection on biopsy. The prostate
health index (phi) is a formula that combines all 3 PSA forms (total PSA, free PSA, and p2PSA) into a single score. phi is calculated using the following formula: (p2PSA/free PSA) x square root (PSA). In a multicenter study that compared the performance of PSA, free PSA, p2PSA, and phi in men undergoing prostate biopsy due to a serum PSA concentration between 4 and 10 ng/mL, phi was the best predictor of any prostate cancer, high-grade cancer, and clinically significant cancer. At 95% clinical sensitivity, the clinical specificity of phi was 16.0%, compared to 8.4% for free PSA and 6.5% for PSA. Prostatic biopsy is required for diagnosis of cancer.

**Useful For:** Aids in distinguishing prostate cancer from benign prostate conditions in men with total prostate-specific antigen (PSA) concentrations in the 4 to 10 ng/mL range and digital rectal examination (DRE) findings that are not suspicious for cancer

**Interpretation:** Prostate health index (phi) may be used to determine the probability of prostate cancer on biopsy in men with total PSA in the 4 to 10 ng/mL range. Low phi scores are associated with a lower probability of finding prostate cancer on biopsy and higher phi scores are associated with an increased probability of finding prostate cancer on biopsy. The choice of an appropriate phi score to be used in guiding clinical decision-making may vary for each patient and may depend on other clinically factors or on family history of disease. The table below indicates the probability of finding prostate cancer on biopsy when PSA is in the range of 4 to 10 ng/mL and may be used as guidance for interpreting the phi score. phi Range Probability of Cancer 95% Confidence Interval

<table>
<thead>
<tr>
<th>phi Range</th>
<th>Probability of Cancer</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-26.9</td>
<td>9.8%</td>
<td>5.2-15.4%</td>
</tr>
<tr>
<td>27.0-35.9</td>
<td>16.8%</td>
<td>11.3-22.2%</td>
</tr>
<tr>
<td>36.0-54.9</td>
<td>33.3%</td>
<td>26.8-39.9%</td>
</tr>
<tr>
<td>&gt; or =55.0</td>
<td>50.1%</td>
<td>39.8-61.0%</td>
</tr>
</tbody>
</table>

**Reference Values:**

- **Age**
  - Reference Range
  - < or =2.0 ng/mL
  - 40-49 years < or =2.5 ng/mL
  - 50-59 years < or =3.5 ng/mL
  - 60-69 years < or =4.5 ng/mL
  - 70-79 years < or =6.5 ng/mL
  - > or =80 years < or =7.2 ng/mL

- **PERCENT FREE PSA Males:** When total PSA is in the range of 4-10 ng/mL
  - % Free PSA Probability of Cancer
  - < or = 56%
  - 11-15% 28%
  - 16-20% 20%
  - 21-25% 16%
  - >25% 8%

- **PROSTATE HEALTH INDEX (phi) Males:** When total PSA is in the range of 4-10 ng/mL
  - phi Range Probability of Cancer 95% Confidence Interval
  - 0-26.9 9.8% 5.2-15.4%
  - 27.0-35.9 16.8% 11.3-22.2%
  - 36.0-54.9 33.3% 26.8-39.9%
  - > or =55.0 50.1% 39.8-61.0%

**PSAIM 70543**

**Prostate Specific Antigen (PSA) Immunostain, Technical Component Only**

**Clinical Information:** Prostate specific antigen is present within the cytoplasm of glandular epithelium in normal prostate, as well as in prostate cancer. It is useful diagnostically for identification of adenocarcinoma of the prostate in metastatic sites and for differentiating prostatic adenocarcinoma from urothelial carcinoma.

**Useful For:** Marker of glandular epithelium in normal and neoplastic prostate

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**PROF 62665**

**Prostate Tumor, FISH, Tissue**

**Clinical Information:** The tumor suppressor gene PTEN is often altered in patients with prostate cancer. Patients with advanced tumors have a deletion of the PTEN gene locus. Rearrangement or separation may be another mechanism responsible for inactivation of the PTEN gene. FISH analysis allows for the detection of deletion, homozygous deletion, and rearrangement of the PTEN gene region.

**Useful For:** Identifying PTEN gene deletion or rearrangements in patients with prostatic adenocarcinoma

**Interpretation:** A positive result with the PTEN probe is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result of PTEN suggests inactivating structural alterations of the PTEN gene region at 10q23. A negative result suggests no structural alterations of the locus.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Prostate-Specific Antigen (PSA) Diagnostic, Serum

Clinical Information: Prostate-specific antigen (PSA) is a glycoprotein that is produced by the prostate gland, the lining of the urethra, and the bulbourethral gland. Normally, very little PSA is secreted in the blood. Increases in glandular size and tissue damage caused by benign prostatic hypertrophy, prostatitis, or prostate cancer may increase circulating PSA levels. In patients with previously diagnosed prostate cancer, PSA testing is advocated as an early indicator of tumor recurrence and as an indicator of response to therapy. The role of PSA in early detection of prostate cancer is controversial. The American Cancer Society recommends annual examination with digital rectal examination and serum PSA beginning at age 50, and also for those men with a life expectancy of at least 10 years after detection of prostate cancer. For men in high-risk groups, such as African Americans or men with a first-degree relative diagnosed at a younger age, testing should begin at a younger age. It is generally recommended that information be provided to patients about the benefits and limitations of testing and treatment so they can make informed decisions.

Useful For: Evaluating patients with documented prostate problems in whom multiple prostate-specific antigen tests may be necessary per year Monitoring patients with a history of prostate cancer as an early indicator of recurrence and response to treatment

Interpretation: Prostate-specific antigen (PSA) values are reported with the 95th percentile limits by decade of age. These reference limits include men with benign prostatic hyperplasia. They exclude all cases with proven cancer. PSA values exceeding the age-specific limits are suspicious for prostate disease, but further testing, such as prostate biopsy, is needed to diagnose prostate pathology. The minimal reporting value is 0.1 ng/mL. Values above 0.2 ng/mL are considered evidence of biochemical recurrence of cancer in men after prostatectomy.

Reference Values:

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>PSA Upper Limit (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; or =2.0</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>&lt; or =2.5</td>
</tr>
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prostate gland, the lining of the urethra, and the bulbourethral gland. Normally, very little PSA is secreted in the blood. Increases in glandular size and tissue damage caused by benign prostatic hypertrophy, prostatitis, or prostate cancer may increase circulating PSA levels. In patients with previously diagnosed prostate cancer, PSA testing is advocated as an early indicator of tumor recurrence and as an indicator of response to therapy. The role of PSA in early detection of prostate cancer is controversial. The American Cancer Society recommends annual examination with digital rectal examination and serum PSA beginning at age 50, and also for those men with a life expectancy of at least 10 years after detection of prostate cancer. For men in high-risk groups, such as African Americans or men with a first-degree relative diagnosed at a younger age, testing should begin at a younger age. It is generally recommended that information be provided to patients about the benefits and limitations of testing and treatment so they can make informed decisions.

**Useful For:** Monitoring patients with a history of prostate cancer as an early indicator of recurrence and response to treatment Prostate cancer screening

**Interpretation:** Prostate-specific antigen (PSA) values are reported with the 95th percentile limits by decade of age. These reference limits include men with benign prostatic hyperplasia. They exclude all cases with proven cancer. PSA values exceeding the age-specific limits are suspicious for prostate disease, but further testing, such as prostate biopsy, is needed to diagnose prostate pathology. The minimal reporting value is 0.1 ng/mL. Values above 0.2 ng/mL are considered evidence of biochemical recurrence of cancer in men after prostatectomy.

**Reference Values:**

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<tr>
<th>Age (Years)</th>
<th>PSA Upper Limit (ng/mL)</th>
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identifying cases of early biochemical recurrence and for selecting patients with adverse clinicopathologic risk factors for secondary therapy. However, some authors believe that USPSA assays offers minimal advantages and could lead to increased anxiety in patients who have clinically meaningless rises of PSA and might lead to overtreatment.

**Useful For:** Monitoring disease after radical prostatectomy. This test should not be used for initial prostate cancer screening.

**Interpretation:** An undetectable (<0.01 ng/mL) ultrasensitive prostate-specific antigen (PSA) concentration after radical prostatectomy is reassuring and may aid in postoperative risk stratification of patients. A detectable PSA concentration (> or =0.01 ng/mL) after radical prostatectomy does not necessarily translate into disease progression or recurrence. Interpretation of a detectable PSA needs to be made in conjunction with other clinicopathologic risk factors. The cutpoint for interpretation of ultrasensitive PSA assays remains controversial and has ranged from 0.01 to 0.05 ng/mL. For example, in a study that included 754 men after RP, a cutoff of 0.01 ng/mL was an independent predictor of BCR. BCR-free survival at 5 years was 92.4% for patients with a PSA post-RP of less than 0.01 ng/mL and 56.8% for patients with a PSA post-RP of 0.01 ng/mL or higher. In the same study a cutoff of 0.03 ng/mL also predicted BCR independent of clinicopathological factors and BCR-free survival at 5 yrs was 90.8% for patients with a PSA post-RP of less than 0.03 ng/mL and 26.9% for patients with a PSA post-RP of greater or equal to 0.03 ng/mL. (1)

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**Clinical References:**

**Prostate-Specific Antigen (PSA), Total and Free, Serum**

**Clinical Information:** Prostate-specific antigen (PSA) is a glycoprotein that is produced by the prostate gland, the lining of the urethra, and the bulbourethral gland. Normally, very little PSA is secreted in the blood. Increases in glandular size and tissue damage caused by benign prostatic hypertrophy, prostatitis, or prostate cancer may increase circulating PSA levels. PSA exists in serum in multiple forms: complexed to alpha-1-anti-chymotrypsin (PSA-ACT complex), unbound (free PSA), and enveloped by alpha-2-macroglobulin (not detected by immunoassays). Higher total PSA levels and lower percentages of free PSA are associated with higher risks of prostate cancer. Most prostate cancers are slow growing, so the utility of prostate cancer screening is marginal in most men with a life expectancy of less than 10 years.

**Useful For:** The percentage of measured prostate-specific antigen (PSA) existing in the free form (free:total PSA ratio) is useful in assessing the risk of prostate cancer in patients with borderline or moderately increased total PSA (4.0-10.0 ng/mL) and has been used to help select men who should have...
**Interpretation:** When total prostate-specific antigen (PSA) concentration is below 2.0 ng/mL, the probability of prostate cancer in asymptomatic men is low, further testing and free PSA may provide little additional information. When total PSA concentration is above 10.0 ng/mL, the probability of cancer is high and prostate biopsy is generally recommended. The total PSA range of 4.0 to 10.0 ng/mL has been described as a diagnostic "gray zone," in which the free:total PSA ratio helps to determine the relative risk of prostate cancer (see table below). Therefore, some urologists recommend using the free:total ratio to help select which men should undergo biopsy. However, even a negative result of prostate biopsy does not rule-out prostate cancer. Up to 20% of men with negative biopsy results have subsequently been found to have cancer. Based on free:total PSA ratio: the percent probability of finding prostate cancer on a needle biopsy by age in years: Free:total PSA ratio 50-59 years 60-69 years > or =70 years < or =0.10 49.2% 57.5% 64.5% 0.11-0.18 26.9% 33.9% 40.8% 0.19-0.25 18.3% 23.9% 29.7% >0.25 9.1% 12.2% 15.8%

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Females: not applicable

**Clinical References:**

**Prostatic Acid Phosphatase (PACP) Immunostain, Technical Component Only**

**Clinical Information:** Prostatic acid phosphatase (PACP) is a cytoplasmic enzyme produced in normal prostatic epithelium and prostatic adenocarcinoma. PACP is a useful adjunct to the immunostain for prostate-specific antigen; if 1 of these 2 markers is immunoreactive, a tumor of prostatic origin is likely. Bladder epithelium and certain neuroendocrine tumors such as rectal carcinoid may be weakly immunoreactive.

**Useful For:** Enzyme produced in normal prostatic epithelium and prostatic adenocarcinoma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation
for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**Prostatic Acid Phosphatase (PAP), Serum**

**Clinical Information:** Prostatic acid phosphatase (PAP), a glycoprotein synthesized by the prostate gland, is a member of a diverse group of isoenzymes, the acid phosphatases, which are capable of hydrolyzing phosphate esters in acidic medium. They are classified on the basis of their electrophoretic mobilities. PAP was a major tumor marker for prostate cancer for more than 50 years.(1) However, PAP is no longer used to screen for or stage prostate cancer. In most instances, serum prostate specific antigen (PSA) is used instead. PAP usefulness is now limited to niche applications. Pre-treatment PAP measurement may add unique, clinically useful prognostic information for predicting recurrence in men who are undergoing radical prostatectomy for clinically localized prostate cancer. PAP also may be useful for following the progression of disease response to therapy in men treated by androgen ablation. However, for both of these applications, PSA provides more information and also should be utilized.

**Useful For:** Predicting recurrence after radical prostatectomy for clinically localized prostate cancer and following response to androgen ablation therapy, when used in conjunction with prostate-specific antigen

**Interpretation:** Prostatic acid phosphatase (PAP) levels above the reference range may indicate prostate cancer, but can be due to many other factors, see Cautions. A rise in PAP levels in patients with known prostate cancer can indicate tumor progression or recurrence. However, there is considerable intra-subject biological variability, limiting the usefulness of this test.

**Reference Values:**< or =2.1 ng/mL


**Protein C Activity, Plasma**

**Clinical Information:** Physiology: Protein C is a vitamin K-dependent anticoagulant proenzyme. It is synthesized in the liver and circulates in the plasma. The biological half-life of plasma protein C is approximately 6 to 10 hours, similar to the relatively short half-life of coagulation factor VII. Protein C is activated by thrombin, in the presence of an endothelial cell cofactor (thrombomodulin), to form the active enzyme activated protein C (APC). APC functions as an anticoagulant by proteolytically inactivating the activated forms of coagulation factors V and VIII (factors Va and VIIIa). APC also enhances fibrinolysis by inactivating plasminogen activator inhibitor (PAI-1). Expression of the anticoagulant activity of APC is enhanced by a cofactor, protein S, another vitamin K-dependent plasma protein. Pathophysiology: Congenital homozygous protein C deficiency results in a severe thrombotic
diathesis, evident in the neonatal period and resembling purpura fulminans. Congenital heterozygous protein C deficiency may predispose to thrombotic events, primarily venous thromboembolism; arterial thrombosis (stroke, myocardial infarction, etc.) may occur. Some individuals with hereditary heterozygous protein C deficiency may have no personal or family history of thrombosis and may or may not be at increased risk. Congenital heterozygous protein C may predispose to development of coumarin-associated skin necrosis. Skin necrosis has occurred during the initiation of oral anticoagulant therapy. Two types of hereditary heterozygous protein C deficiency are recognized: -Type I (concordantly decreased protein C function and antigen) -Type II (decreased protein C function with normal antigen level). Acquired deficiencies of protein C may occur in association with: -Vitamin K deficiency -Oral anticoagulation with coumarin compounds -Liver disease -Intravascular coagulation and fibrinolysis/disseminated intravascular coagulation (ICF/DIC) The clinical hemostatic significance of acquired protein C deficiency is uncertain. Assay of protein C functional activity is recommended for the initial laboratory evaluation of patients suspected of having congenital protein C deficiency (personal or family history of thrombotic diathesis), rather than assay of protein C antigen (PCAG / Protein C Antigen, Plasma).

Useful For: As an initial test for evaluating patients suspected of having congenital protein C deficiency, including those with personal or family histories of thrombotic events. Because coagulation testing and its interpretation is complex, Mayo Medical Laboratories suggests ordering THRMP / Thrombophilia Profile. Detecting and confirming congenital Type I and Type II protein C deficiencies, detecting and confirming congenital homozygous protein C deficiency, and identifying decreased functional protein C of acquired origin (eg, due to oral anticoagulant effect, vitamin K deficiency, liver disease, intravascular coagulation and fibrinolysis/disseminated intravascular coagulation.)

Interpretation: Values <60% to 70% may represent a congenital deficiency state, if acquired deficiencies can be excluded. Protein C activity (and antigen) is generally undetectable in individuals with severe, homozygous protein C deficiency. Oral anticoagulant therapy (warfarin, Coumadin) decreases protein C activity, compromising the ability to distinguish between congenital and acquired protein C deficiency. Comonitent measurement of the activity of coagulation factor VII (or factor X) may aid in differentiating congenital deficiency state from acquired protein C deficiency due to oral anticoagulant effect, but the ratio of the activities of protein C:factor VII (or factor X) has not been demonstrated to provide certainty about this distinction. The clinical significance of acquired protein C deficiency and of increased protein C is unknown.

Reference Values:
Adults: 70%-150%
Normal, full-term newborn infants or healthy premature infants may have decreased levels of protein C activity (15%-50%), which may not reach adult levels until later in childhood or early adolescence.*

*See Pediatric Hemostasis References in Coagulation Studies in Special Instructions.

Clinical References:

PCAG 9127

Protein C Antigen, Plasma

Clinical Information: Physiology: Protein C is a vitamin K-dependent anticoagulant proenzyme. It is synthesized in the liver and circulates in the plasma. The biological half-life of plasma protein C is approximately 6 to 10 hours, similar to the relatively short half-life of coagulation factor VII. Protein C is
activated by thrombin, in the presence of an endothelial cell cofactor (thrombomodulin), to form the active enzyme, activated protein C (APC). APC functions as an anticoagulant by proteolytically inactivating the activated forms of coagulation factors V and VIII (factors Va and VIIIa). APC also enhances fibrinolysis by inactivating plasminogen activator inhibitor (PAI-1). Expression of the anticoagulant activity of APC is enhanced by a cofactor, protein S, another vitamin K-dependent plasma protein. Pathophysiology: Congenital homozygous protein C deficiency results in a severe thrombotic diathesis, evident in the neonatal period and resembling purpura fulminans. Congenital heterozygous protein C deficiency may predispose to thrombotic events, primarily venous thromboembolism. Arterial thrombosis (stroke, myocardial infarction, etc) may occur. Some individuals with hereditary heterozygous protein C deficiency may have no personal or family history of thrombosis and may or may not be at increased risk. The 2 types of hereditary heterozygous protein C deficiencies that are recognized are: -Type I (concordantly decreased protein C function and antigen) -Type II (decreased protein C function with normal antigen) Acquired deficiency of protein C may occur in association with: -Vitamin K deficiency -Oral anticoagulation with coumarin compounds -Liver disease -Intravascular coagulation and fibrinolysis/disseminated intravascular coagulation (ICF/DIC)

**Useful For:** Differentiating congenital Type I protein C deficiency from Type II deficiency
Evaluating the significance of decreased functional protein C, especially when decreased protein C activity might be congenital rather than acquired (eg, due to oral anticoagulant effect, vitamin K deficiency, liver disease, or intravascular coagulation and fibrinolysis/disseminated intravascular coagulation)

**Interpretation:** Values <70% to 75% may represent a congenital deficiency state, if acquired deficiencies can be excluded. Protein C antigen and activities generally are undetectable in individuals with severe, homozygous protein C deficiency. Acquired protein C deficiency is of uncertain clinical hemostatic significance. Clinical significance of increased protein C is unknown.

**Reference Values:**
Adults: 70%-150%
Normal, full-term newborn infants or healthy premature infants may have decreased levels of protein C antigen (15%-50%), which may not reach adult levels until later in childhood or early adolescence.*
*See Pediatric Hemostasis References in Coagulations Studies in Special Instructions.

**Clinical References:**

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**PCTR 36878**

**Protein Catabolic Rate, 24 Hour, Urine**

**Useful For:**

**Interpretation:**

**Reference Values:**
Only orderable as part of a profile. For more information see SAT24 / Supersaturation Profile, 24 Hour, Urine.

**Clinical References:**
**Protein Electrophoresis**

**Clinical Information:** Serum proteins can be grouped into 5 fractions by protein electrophoresis:
- Albumin, which represents almost two-thirds of the total serum protein
- Alpha-1, composed primarily of alpha-1-antitrypsin (A1AT), an alpha-1-acid glycoprotein
- Alpha-2, composed primarily of alpha-2-macroglobulin and haptoglobin
- Beta, composed primarily of transferrin and C3
- Gamma, composed primarily of immunoglobulins

The concentration of these fractions and the electrophoretic pattern may be characteristic of diseases such as monoclonal gammopathies, A1AT deficiency disease, nephrotic syndrome, and inflammatory processes associated with infection, liver disease, and autoimmune diseases.

**Useful For:** Screening patients with suspected monoclonal gammopathies
Diagnosis of monoclonal gammopathies, when used in conjunction with matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) and free light chains

**Interpretation:**

- **Monoclonal Gammopathies:** A characteristic monoclonal band (M-spike) is often found on serum protein electrophoresis (SPE) in the gamma globulin region and more rarely in the beta or alpha-2 regions. The finding of a M-spike, restricted migration, or hypogammaglobulinemic SPE pattern is suggestive of a possible monoclonal protein and should be confirmed by immunoaffinity-purification matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) to identify the immunoglobulin heavy chain and/or light chain. MPSU / Monoclonal Protein Study, 24 Hour Urine is suggested for first time M-spike-positive patients to assess for renal disease that can be associated with an M-spike. -A monoclonal IgG or IgA greater than 3 g/dL is consistent with multiple myeloma (MM). -A monoclonal IgG or IgA less than 3 g/dL may be consistent with monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis, early or treated myeloma, as well as a number of other monoclonal gammopathies. -A monoclonal IgM greater than 3 g/dL is consistent with macroglobulinemia. -The initial identification of a serum M-spike greater than 1.5 g/dL on SPE should be followed by MPSU / Monoclonal Protein Study, 24 Hour Urine. -The initial identification of an IgM, IgA, or IgG M-spike greater than 4 g/dL, greater than 5 g/dL, and greater than 6 g/dL, respectively, should be followed by VISCS / Viscosity, Serum. After the initial identification of an M-spike, quantitation of the M-spike on follow-up SPE can be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the beta region (most commonly an IgA or an IgM) quantitative immunoglobulin levels may be more a useful tool to follow the monoclonal protein level than SPE. A decrease or increase of the M-spike that is greater than 0.5 g/dL is considered a significant change. Patients suspected of having a monoclonal gammopathy may have normal serum SPE patterns. Approximately 11% of patients with MM have a completely normal serum SPE, with the monoclonal protein only identified by MALDI-TOF MS. Approximately 8% of MM patients have hypogammaglobulinemia without a quantifiable M-spike on SPE but identified by MALDI-TOF MS. Accordingly, a normal serum SPE does not rule out the disease and should not be used to screen for the disorder. The SMOGA / Monoclonal Gammopathy Screen, Serum, which includes MALDI-TOF MS and immunoglobulin free light chains, should be performed to screen if the clinical suspicion is high. Other Abnormal SPE Findings: -A qualitatively normal but elevated gamma fraction (polyclonal hypergammaglobulinemia) is consistent with infection, liver disease, or autoimmune disease. -A depressed gamma fraction (hypogammaglobulinemia) is consistent with immune deficiency and can also be associated with primary amyloidosis or nephrotic syndrome. -A decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.1 g/dL), and decreased gamma fraction (<1 g/dL) is consistent with nephrotic syndrome, and when seen in an adult older than 40 years, should be followed by MPSU / Monoclonal Protein Study, 24 Hour Urine. -In the hereditary deficiency of a protein (eg, agammaglobulinemia, alpha-1-antitrypsin [A1AT] deficiency, hypoalbuminemia), the affected fraction is faint or absent. -An absent alpha-1 fraction is consistent with A1AT deficiency disease and should be followed by a quantitative A1AT assay (AAT / Alpha-1- Antitrypsin, Serum).

**Reference Values:**

Only orderable as part of a profile. For more information see:
SPEP / Electrophoresis, Protein, Serum
SPISO / Protein Electrophoresis and Isotype, Serum
SMOGA / Monoclonal Gammopathy Screen, Serum

**Protein Electrophoresis and Isotype, Serum**

**Clinical Information:** This profile includes total protein, protein electrophoresis, and M-protein isotyping. The serum proteins can be grouped into 5 fractions by protein electrophoresis: -Albumin, which represents almost two-thirds of the total serum protein -Alpha-1, composed primarily of alpha-1-antitrypsin (A1AT), an alpha-1-acid glycoprotein -Alpha-2, composed primarily of alpha-2-macroglobulin and haptoglobin -Beta, composed primarily of transferrin and complement C3 -Gamma, composed primarily of immunoglobulins (Ig) The concentration of these fractions and the electrophoretic pattern may be characteristic of diseases such as monoclonal gammopathies, A1AT deficiency disease, nephrotic syndrome, and inflammatory processes associated with infection, liver disease, and autoimmune diseases. The following algorithms are available in Special Instructions: -Laboratory Approach to the Diagnosis of Amyloidosis -Laboratory Screening Tests for Suspected Multiple Myeloma

**Useful For:** Diagnosis of monoclonal gammopathies, when used in conjunction with locally performed serum free light chain studies (performed at client site)

**Interpretation:** Monoclonal Gammopathies: -A characteristic monoclonal band (M-spike) is often found on serum protein electrophoresis (SPE) in the gamma globulin region and, more rarely, in the beta or alpha-2 regions. The finding of an M-spike, restricted migration, or hypogammaglobulinemic SPE pattern is suggestive of a possible monoclonal protein. Immunoaffinity purification followed by matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) is performed to identify any immunoglobulin heavy and light chains present. -A monoclonal IgG or IgA of greater than 3 g/dL is consistent with multiple myeloma (MM). -A monoclonal IgG or IgA of less than 3 g/dL may be consistent with monoclonal gammopathy of undetermined significance (MGUS), primary systemic amyloidosis, early or treated myeloma, as well as a number of other monoclonal gammopathies. -A monoclonal IgM of greater than 3 g/dL is consistent with macroglobulinemia. -The initial identification of a serum M-spike greater than 1.5 g/dL on SPE should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -The initial identification of an IgM, IgA, or IgG M-spike greater than 4 g/dL, greater than 5 g/dL, and greater than 6 g/dL respectively, should be followed by VISCS / Viscosity, Serum. After the initial identification of an M-spike, quantitation of the M-spike on follow-up SPE can be used to monitor the monoclonal gammopathy. However, if the monoclonal protein falls within the beta region (most commonly an IgA or an IgM) quantitative immunoglobulin levels may be more a useful tool to follow the monoclonal protein level than SPE. A decrease or increase of the M-spike that is greater than 0.5 g/dL is considered a significant change. Patients suspected of having a monoclonal gammopathy may have normal serum SPE patterns. Approximately 11% of patients with MM have a completely normal serum SPE, with the monoclonal protein only identified by MALDI-TOF MS. Approximately 8% of MM patients have hypogammaglobulinemia without a quantifiable M-spike on SPE but identified by MALDI-TOF MS. Accordingly, a normal serum SPE does not rule out the disease and SPE should not be used to screen for the disorder. SMOGA / Monoclonal Gammopathy Screening, Serum which includes MALDI-TOF MS and serum free light chains, should be done to screen if the clinical suspicion is high. Other Abnormal SPE Findings: -A qualitatively normal but elevated gamma fraction (polyclonal hypergammaglobulinemia) is consistent with infection, liver disease, or autoimmune disease. -A depressed gamma fraction (hypogammaglobulinemia) is consistent with immune deficiency and can also be associated with primary amyloidosis or nephrotic syndrome. -A decreased albumin (<2 g/dL), increased alpha-2 fraction (>1.1 g/dL), and decreased gamma fraction (<1 g/dL) is consistent with nephritic syndrome and, when seen in an adult older than 40 years, should be followed by MPSU / Monoclonal Protein Study, 24 Hour, Urine. -In the hereditary deficiency of a protein (eg, agammaglobulinemia, alpha-1-antitrypsin
[A1AT] deficiency, hypoalbuminemia), the affected fraction is faint or absent. An absent alpha-1 fraction is consistent with A1AT deficiency disease and should be followed by a quantitative A1AT assay (AAT / Alpha-1-Antitrypsin, Serum).

Reference Values:
TOTAL PROTEIN
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients that are <12 months of age.

PROTEIN ELECTROPHORESIS
Albumin: 3.4-4.7 g/dL
Alpha-1-globulin: 0.1-0.3 g/dL
Alpha-2-globulin: 0.6-1.0 g/dL
Beta-globulin: 0.7-1.2 g/dL
Gamma-globulin: 0.6-1.6 g/dL
An interpretive comment is provided with the report.
Reference values have not been established for patients that are <16 years of age.

M-PROTEIN ISOTYPE MALDI-TOF MS, S
No monoclonal protein detected


Protein S Activity, Plasma
Clinical Information: Protein S is a vitamin K-dependent plasma glycoprotein synthesized predominantly within the liver. Protein S is also synthesized in endothelial cells and present in platelets. As a part of the plasma anticoagulant system, protein S acts as a necessary cofactor to activated protein C (APC) in the proteolytic inactivation of procoagulant factors Va and VIIIa. About 60% of the total plasma protein S antigen circulates bound to C4b binding protein (C4b-BP), while the remainder circulates as "free" protein S. Only free protein S has anticoagulant activity. Congenital protein S deficiency is an autosomal codominant disorder that is present in 1% to 3% of patients with venous thromboembolism. Heterozygous protein S deficiency carriers have approximately a 10-fold increased risk of venous thromboembolism. Other phenotypic expressions of heterozygous congenital protein S deficiency include recurrent miscarriage, complications of pregnancy (preeclampsia, abruptio placenta, intrauterine growth restriction, and stillbirth) and possibly arterial thrombosis. Three types of heterozygous congenital protein S deficiency have been described according to the levels of total protein S antigen, free protein S antigen, and protein S (APC cofactor) activity in plasma. Types of Heterozygous Protein S Deficiency Type Protein S Antigen, Free Protein S Antigen, Total Protein Activity I Decreased Decreased Decreased II Normal Normal Decreased Decreased Normal Decreased Type I and III protein S deficiency are much more common than type II (dysfunctional) protein S deficiency. Type III protein S deficiency appears to be partly due to mutations within the protein S binding region for C4b-BP. Homozygous protein S deficiency is rare, but can present as neonatal purpura fulminans, reflecting severe intravascular coagulation and fibrinolysis/disseminated intravascular coagulation (ICF/DIC) caused by the absence or near absence of plasma protein S. Acquired deficiency of protein S is much more common than hereditary protein S deficiency and is generally of unknown hemostatic significance (ie, uncertain thrombosis risk). Among the many causes of acquired protein S deficiency are: -Vitamin K deficiency -Oral anticoagulant therapy -Acute illness (eg, acute thrombosis, recent surgery, or other disorder associated with acute inflammation) -Liver disease -ICF/DIC -Thrombotic thrombocytopenic purpura -Pregnancy, oral contraceptive, or estrogen therapy -Nephrotic syndrome -Sickle cell anemia

Useful For: Second-order testing for diagnosis of congenital or acquired protein S deficiency for example, as an adjunct to initial testing based on results of protein S antigen assay (free protein S antigen,
with or without total protein S antigen assay) Evaluating patients with a history of venous thromboembolism

**Interpretation:** In type I and type III congenital deficiency, free protein S antigen is decreased and protein S functional activity is similarly decreased. In type II congenital (dysfunctional) protein S deficiency, total and free protein S antigen levels are normal but functional activity is decreased. Patients with acquired free protein S deficiency associated with inflammation-related increase of C4b-binding protein (C4b-BP) typically have decreased free protein S antigen (and protein S activity) and normal (or elevated) total protein S antigen. Acquired protein S deficiency is of uncertain clinical hemostatic significance and is associated with a variety of conditions. Elevated protein S levels are of uncertain clinical significance.

**Reference Values:**
- **Males:** 65-160%
- **Females**
  - <50 years: 50-160%
  - ≥50 years: 65-160%

Newborn infants have normal or near-normal free protein S antigen (≥50%), although total protein S antigen is usually below the adult reference range. There are insufficient data concerning protein S activity in normal neonates, infants, and children; but normal or near-normal activity (≥50%) probably is present by age 3 to 6 months.

**Clinical References:**

**Clinical Information:** Protein S is a vitamin K-dependent glycoprotein present in platelets and synthesized within the liver and endothelial cells. Protein S works as part of the natural anticoagulant system by acting as a cofactor to activated protein C (APC) in the proteolytic inactivation of procoagulant factors Va and VIIIa. In addition, protein S has direct APC-independent anticoagulant activity by inhibiting formation of the prothrombin and tenase complexes, possibly due to its high affinity for anionic phospholipid membranes. In human plasma, protein S forms a complex with the complement regulatory protein, C4b-binding protein (C4bBP). Of the total plasma protein S, approximately 60% circulates bound to C4bBP while the remaining 40% circulates as "free" protein S. Only free protein S has anticoagulant function. C4bBP is composed of 6 or 7 alpha-chains and 1 or no beta-chain (C4bBP-beta). Different C4bBP isoforms are present in plasma, but only C4bBP-beta binds protein S. Congenital protein S deficiency is an autosomal dominant disorder that is present in 2% to 6% of patients with venous thrombosis. Patients with protein S deficiency have an approximately 10-fold increased risk of venous thrombosis. In addition they may also experience recurrent miscarriage, complications of pregnancy (preeclampsia, abruptio placenta, intrauterine growth restriction, and stillbirth) and possibly arterial thrombosis. Three types of protein S deficiency have been described according to the levels of total protein S antigen, free protein S antigen, and protein S activity in plasma. Types I and III protein S deficiency are much more common than type II (dysfunctional) protein S deficiency. Type III protein S deficiency appears to be partly due to mutations within the protein S binding region for C4bBP-beta. Homozygous protein S deficiency is rare, but can present as neonatal purpura fulminans, reflecting severe disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF) caused by the absence of plasma
Acquired deficiency of protein S has causes that are generally of unknown haemostatic significance (ie, uncertain thrombosis risk), and is much more common than hereditary protein S deficiency. Acquired protein S deficiency can present through vitamin K deficiency, oral anticoagulant therapy, liver disease, DIC/ICF, thrombotic thrombocytopenia purpura, pregnancy or estrogen therapy, nephritic syndrome, and sickle cell anemia. As an acute-phase reactant, plasma C4bBP levels increase with acute illness and may cause acquired free protein S deficiency. Measurement of plasma free protein S antigen is performed as the initial testing for protein S deficiency. When the free protein S antigen level is below the age- and sex-adjusted normal range, reflexive testing will be performed for total plasma protein S antigen.

**Useful For:** Investigation of patients with a history of thrombosis

**Interpretation:** Protein S values vary widely in the normal population and are age- and sex-dependent.

<table>
<thead>
<tr>
<th>Types of Heterozygous Protein S Deficiency</th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein S Antigen</td>
<td>Low</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>Free Protein S Antigen</td>
<td>Low</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>Total Protein S Activity</td>
<td>I Low</td>
<td>Low II Normal</td>
<td>Low III Low</td>
</tr>
</tbody>
</table>

Protein S and C4bBP are coordinately regulated, and an increased total protein S antigen and low free protein S antigen most commonly reflect acute or chronic inflammation or illness with an associated increase in plasma C4bBP. For patients in whom hereditary protein S deficiency is strongly suspected and the free plasma protein S antigen level is normal, consideration should be given to testing of free protein S activity, S_FX / Protein S Activity, Plasma, for detecting type II protein S deficiency (which is rare). An increased total protein S antigen is of uncertain clinical significance because free protein S antigen levels are usually normal, in such situations. However, the total protein S antigen level may be helpful in distinguishing acquired versus congenital protein S deficiency. High normal or increased total protein S antigen and reduced free protein S antigen suggests acquired protein S deficiency, as may be seen in pregnancy or inflammation. In contrast, low normal or decreased total protein S antigen and reduced free protein S antigen suggests vitamin K deficiency or a warfarin effect, but also could reflect congenital protein S deficiency (type I or III). Vitamin K deficiency, oral anticoagulant therapy, presence of liver disease, or disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF) are common acquired causes of protein S deficiency, which is of uncertain significance when such conditions are present.

Concomitant assay of coagulation factor II activity may be helpful in differentiating congenital protein S deficiency from oral anticoagulation effects, but supportive data are currently suboptimal. Differentiation of congenital and acquired protein S deficiency requires clinical correlation and may require repeated laboratory study of the patient and selected family members in some instances. DNA-based testing may be helpful, but is generally not yet available.

**Reference Values:**

**TOTAL**
- Males: 80-160%
- Females
  - <50 years: 70-160%
  - ≥50 years: 80-160%

**FREE**
- Males: 65-160%
- Females
  - <50 years: 50-160%
  - ≥50 years: 65-160%

Normal, full-term newborn infants or healthy premature infants may have decreased levels of total protein S (15-50%); but because of low levels of C4bBP, free protein S may be normal or near the normal adult level (> or =50%). Total protein S reaches adult levels by 90 to 180 days postnatal.*

**Clinical References:**

**12PTU**

**Protein, Total, 12 Hour, Urine**

**Clinical Information:** Protein in urine normally consists of plasma proteins that have been filtered by glomeruli and not reabsorbed by the proximal tubule, and proteins secreted by renal tubules or other accessory glands. Increased amounts of protein in the urine may be due to: -Glomerular proteinuria: defects in permselectivity of the glomerular filtration barrier to plasma proteins (eg, glomerulonephritis or nephrotic syndrome) -Tubular proteinuria: incomplete tubular reabsorption of proteins (eg, interstitial nephritis) -Overflow proteinuria: increased plasma concentration of proteins that exceeds capacity for proximal tubular reabsorption (eg, multiple myeloma, myoglobinuria) -Urinary tract inflammation or tumor -Preeclampsia -Orthostatic proteinuria In pregnant women, a urinary protein excretion of more than 300 mg/24 hours is frequently cited as consistent with preeclampsia, and 12-hour total protein excretion highly correlates with 24-hour values in this patient population. Orthostatic proteinuria is characterized by increased protein excretion in the upright position, but normal levels when supine. This condition can be detected by comparing urine protein levels in a collection split between day and night (see OPTU / Orthostatic Protein, Timed Collection, Urine). Orthostatic proteinuria is common in childhood and adolescence, but rare after age 30.

**Useful For:** Evaluation of renal disease Screening for monoclonal gammopathy Screening for postural (orthostatic) proteinuria In select clinical situations, collection of a 12-hour specimen may allow more rapid detection of proteinuria states (eg, screening pregnant patients for preeclampsia)

**Interpretation:** Total urine protein determined to be greater than 500 mg/24 hours should be evaluated by immunofixation to assess if there is a monoclonal immunoglobulin light chain and, if present, identify it as either kappa or lambda type. Urinary protein levels may rise to 300 mg/24 hours in healthy individuals after vigorous exercise. Low-grade proteinuria may be seen in inflammatory or neoplastic processes involving the urinary tract.

**Reference Values:**

<163 mg/12 hours (day or night collection)

Reference values have not been established for patients <18 years of age.


**PTU**

**Protein, Total, 24 Hour, Urine**

**Clinical Information:** Protein in urine is normally composed of a combination of plasma-derived proteins that have been filtered by glomeruli and have not been reabsorbed by the proximal tubules and proteins secreted by renal tubules or other accessory glands. Increased amounts of protein in the urine may be due to: -Glomerular proteinuria: caused by defects in permselectivity of the glomerular filtration
barrier to plasma proteins (eg, glomerulonephritis or nephrotic syndrome) -Tubular proteinuria: caused by incomplete tubular reabsorption of proteins (eg, interstitial nephritis) -Overflow proteinuria: caused by increased plasma concentration of proteins (eg, multiple myeloma, myoglobinurin) -Urinary tract inflammation or tumor

**Useful For:** Evaluation of renal disease Screening for monoclonal gammopathy

**Interpretation:** Total protein greater than 500 mg/24 hours should be evaluated by immunofixation to determine if a monoclonal immunoglobulin light chain is present, and if so, identify it as either kappa or lambda type. Urinary protein levels may rise to 300 mg/24 hours in healthy individuals after vigorous exercise. Low-grade proteinuria may be seen in inflammatory or neoplastic processes involving the urinary tract.

**Reference Values:**
- <229 mg/24 hours
  - Reference values have not been established for patients <18 years of age.
  - Reference value applies to 24-hour collection.

**Clinical References:**

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**TPBF 8420**

**Protein, Total, Body Fluid**

**Clinical Information:** Pleural fluid: Pleural fluid is normally present within the pleural cavity surrounding the lungs, serving as a lubricant between the lungs and inner chest wall. Pleural effusion develops when the pleural cavity experiences an overproduction of fluid due to increased capillary hydrostatic and osmotic pressure that exceeds the ability of the lymphatic or venous system to return the fluid to circulation. Laboratory-based criteria are often used to classify pleural effusions as either exudative or transudative. Exudative effusions form due to infection or inflammation of the capillary membranes allowing excess fluid into the pleural cavity. Patients with these conditions benefit from further investigation and treatment of the local cause of inflammation. Transudative effusions form due to systemic conditions such as volume overload, end stage renal disease, and heart failure that can lead to excess fluid accumulation in the pleural cavity. Patients with transudative effusions benefit from treatment of the underlying condition.(1) Dr. Richard Light derived criteria in the 1970s for patients with pleural effusions that are still used today.(2) The criteria include the measurement of total protein and lactate dehydrogenase (LD) in pleural fluid and serum. Exudates are defined as meeting one of the following criteria: 1) pleural fluid-to-serum protein ratio above 0.5 2) pleural fluid LD above two-thirds the upper limit of normal serum LD 3) pleural fluid-to-serum LD ratio above 0.6 Lightâ€™s criteria were designed to be sensitive for detecting exudates at the expense of specificity.(3) Heart failure and recent diuretic use contribute to most misclassifications by Lightâ€™s criteria (transudates falsely categorized as exudates). Serum-to-fluid protein gradient (serum protein minus fluid protein) may be calculated in these cases and when more than 3.1 g/dL suggests the patient has a transudative effusion. Peritoneal fluid: The pathologic accumulation of fluid within the peritoneal cavity is commonly referred to as ascites. The most common cause of ascites is liver cirrhosis. Differentiating cardiac from cirrhotic ascites is a common clinical conundrum as they are common conditions presenting with elevated serum ascites albumin gradient (SAAG). Heart failure leads to the development of high gradient ascites due to hepatic sinusoidal hypertension. Since the sinusoids are normal and have not been damaged from collagen deposition associated with cirrhosis, protein tends to â€œleakâ€• more readily into ascites and is associated with higher total protein concentrations.

**Useful For:** Pleural fluid: Identification of exudative pleural effusions Peritoneal fluid: Differentiating hepatic from other causes of ascites that have elevated serum ascites albumin gradient (SAAG)
**Interpretation:** Pleural fluid: Exudative pleural fluid total protein to serum total protein ratio is typically more than 0.5. Transudative pleural effusions misclassified as exudates have serum protein minus pleural fluid protein more than 3.1 g/dL. Peritoneal fluid: Total protein may be greater than 2.5 g/dL in patients with high albumin gradient ascites caused by heart failure. Other fluids: Total protein may be used to differentiate transudative from exudative effusions. The decision limits are not well defined in fluids other than pleural fluid and should be interpreted in conjunction with other clinical findings.

**Reference Values:**
Not applicable

**Clinical References:**

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**Protein, Total, Serum**

**Clinical Information:** Plasma proteins are synthesized predominantly in the liver; immunoglobulins are synthesized by mononuclear cells of lymph nodes, spleen and bone marrow. The 2 general causes of alterations of serum total protein are a change in the volume of plasma water and a change in the concentration of 1 or more of the specific proteins in the plasma. Of the individual serum proteins, albumin is present in such high concentrations that low levels of this protein alone may cause hypoproteinemia. Hemoconcentration (decrease in the volume of plasma water) results in relative hyperproteinemia; hemodilution results in relative hypoproteinemia. In both situations, concentrations of all the individual plasma proteins are affected to the same degree. Hyperproteinemia may be seen in dehydration due to inadequate water intake or to excessive water loss (eg, severe vomiting, diarrhea, Addison disease, and diabetic acidosis) or as a result of increased production of proteins. Increased polyclonal protein production is seen in reactive, inflammatory processes; increased monoclonal protein production is seen in some hematopoietic neoplasms (eg, multiple myeloma, Waldenstrom macroglobulinemia, monoclonal gammopathy of undetermined significance).

**Useful For:** Diagnosis and treatment of a variety of diseases involving the liver, kidney, or bone marrow, as well as other metabolic or nutritional disorders

**Interpretation:** Mild hyperproteinemia may be caused by an increase in the concentration of specific proteins normally present in relatively low concentration, eg, increases in acute phase reactants and polyclonal immunoglobulins produced in inflammatory states, late-stage liver disease, and infections. Moderate-to-marked hyperproteinemia may also be due to multiple myeloma and other malignant paraproteinemias, although normal total protein levels do not rule out these disorders. A serum protein electrophoresis should be performed to evaluate the cause of the elevated serum total protein. Hypoproteinemia may be due to decreased production (eg, hypogammaglobulinemia) or increased protein loss (eg, nephrotic syndrome, protein-losing enteropathy). A serum protein electrophoresis should be performed to evaluate the cause of the decreased serum total protein. If a nephrotic pattern is identified, urine protein electrophoresis should also be performed.

**Reference Values:**
> or =1 year: 6.3-7.9 g/dL
Reference values have not been established for patients who are <12 months of age.

**Clinical References:**
**Protein, Total, Spinal Fluid**

**Clinical Information:** Cerebrospinal fluid (CSF) proteins are those that remain in CSF following the ultrafiltration of plasma through the choroidal capillary wall. Some proteins that are unique to CSF are synthesized in the central nervous system. In general, diseases that interrupt the integrity of the capillary endothelial barrier lead to an increase in the total CSF protein. CSF protein is generally increased in all types of meningitis, cerebral infarction, brain abscess, meningoencephalitis, subarachnoid hemorrhage, some brain tumors, trauma to the brain, some cases of multiple sclerosis, encephalomyelitis, and degenerative neurologic diseases. A decreased CSF protein may occur in water intoxication, CSF leak (CSF rhinorrhea or otorrhea), and hyperthyroidism.

**Useful For:** Detecting disruptions of the blood-brain barrier or intrathecal synthesis of immunoglobulins

**Interpretation:** Striking elevations of cerebrospinal fluid (CSF) total protein are noted in bacterial meningitis; smaller elevations occur in the other inflammatory diseases and with tumor or hemorrhage. The effect of any of these conditions is that the proportions of specific proteins in CSF increasingly resemble serum. In order to assess increased permeability or increased intrathecal production of proteins, simultaneous serum specimen and CSF specimens should be taken.

**Reference Values:**

> or =12 months: 0-35 mg/dL

Reference values have not been established for patients that are <12 months of age.


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**Protein:Creatinine Ratio, Random, Urine**

**Clinical Information:** Protein in urine is normally composed of a combination of plasma-derived proteins that have been filtered by glomeruli and have not been reabsorbed by the proximal tubules and proteins secreted by renal tubules or other accessory glands. Increased amounts of protein in the urine may be due to: -Glomerular proteinuria: caused by defects in permselectivity of the glomerular filtration barrier to plasma proteins (eg, glomerulonephritis or nephrotic syndrome) -Tubular proteinuria: caused by incomplete tubular reabsorption of proteins (eg, interstitial nephritis) -Overflow proteinuria: caused by increased plasma concentration of proteins (eg, multiple myeloma, myoglobinuria)

**Useful For:** Evaluation of renal disease Screening for monoclonal gammopathy

**Interpretation:** Total protein of greater than 500 mg/24 hours should be evaluated by immunofixation to determine if a monoclonal immunoglobulin light chain is present and, if so, identify it as either kappa or lambda type. Urinary protein levels may rise to 300 mg/24 hours in healthy individuals after vigorous exercise. Low-grade proteinuria may be seen in inflammatory or neoplastic processes involving the urinary tract. In a random urine specimen, a protein:creatinine or protein:osmolality ratio can be used to roughly approximate 24-hour excretion rates. The normal protein-to-osmolality ratio is less than 0.42.(1) For patients younger than 18 years of age no reference range has been established.

**Reference Values:**

<0.18 mg/mg creatinine

Reference values have not been established for patients <18 years of age.


**Proteinase 3 Antibodies, IgG, Serum**

**Clinical Information:** Proteinase 3 (PR3) antigen is a 29kD serine protease that exists as a protein triplet in human neutrophils. Wegener granulomatosis (WG) is an autoimmune vasculitis that affects the kidneys and lungs, as well as other organs. Patients with WG develop autoantibodies to the PR3 antigen of myeloid lysosomes (PR3 antineutrophil cytoplasmic antibodies [PR3 ANCA]).

Since it is often impossible to distinguish between WG and other forms of vasculitis on the basis of clinical signs and symptoms, tests for PR3 ANCA should be employed with other serologic tests in the initial diagnostic evaluation of patients with clinical features of vasculitis (eg, VASC / Antineutrophil Cytoplasmic Antibodies Vasculitis Panel, Serum).

**Useful For:** Evaluating patients suspected of having Wegener granulomatosis (WG) Distinguishing between WG and other forms of vasculitis, in conjunction with MPO / Myeloperoxidase Antibodies, IgG, Serum and ANCA / Cytoplasmic Neutrophil Antibodies, Serum (may be obtained as VASC / Antineutrophil Cytoplasmic Antibodies Vasculitis Panel, Serum) May be useful to follow treatment response or to monitor disease activity in patients with myeloperoxidase antibodies

**Interpretation:** Proteinase 3 antineutrophil cytoplasmic antibodies (PR3 ANCA) are detectable in nearly all patients with severe active Wegener granulomatosis (WG).

The presence of PR3 ANCA is specific diagnostic indicator of WG; <2% of positive results occur in patients who do not have the disease. A negative result for PR3 ANCA diminishes the likelihood that a patient has active WG; but, approximately 20% of patients with limited WG may test negative for PR3 ANCA.

The levels of PR3 ANCA often decline following successful treatment of patients with WG. Nevertheless, follow-up testing for PR3 ANCA to evaluate clinical status in treated patients should be used with caution as the levels of antibodies may correlate poorly with clinical status in some patients.

**Reference Values:**

<0.4 U (negative)

0.4-0.9 U (equivocal)

> or =1.0 U (positive)

Reference values apply to all ages.

**Clinical References:**


**Prothrombin Fragment 1+2**

**Reference Values:**

87 - 325 pmol/L

Pre-analytical conditions such as a difficult draw may spuriously increase test results.
Prothrombin G20210A Mutation, Blood

Clinical Information: Venous thromboembolism (VTE) is a syndrome of deep vein thrombosis and its complication, pulmonary embolism. The prothrombin (PT) G20210A mutation (F2 rs1799963) is a common polymorphism within the 3’ untranslated region of the prothrombin gene, affecting 1.5% to 3% of Caucasian Americans, especially persons of southern European ancestry. The PT G20210A allele is uncommon among African Americans (carrier frequency of 0.4%). The PT G20210A mutation is associated with a 3-fold increased risk of venous thromboembolism due to increased plasma prothrombin activity among carriers. The PT G20210A gene mutation test is a direct mutation analysis of patient blood leukocyte genomic DNA. At present, there are no other methods of detecting this VTE risk factor except for direct mutation testing.

Useful For: Direct mutation analysis for the prothrombin (PT) G20210A allele should be reserved for patients with clinically suspected thrombophilia. There may be additional indications for direct PT G20210A mutation testing, such as in determining the duration of anticoagulation therapy of venous thromboembolism patients and screening for women contemplating hormone therapy.

Interpretation: The interpretive report will include sample information, assay information, background information, and conclusions drawn from the test results (normal, heterozygous prothrombin [PT] G20210A, homozygous PT G20210A).

Reference Values:
Negative


Prothrombin Time (PT), Plasma

Clinical Information: This assay is used to monitor oral anticoagulant therapy to maintain a patient in a safe therapeutic range. In the absence of oral anticoagulant therapy, a prolonged prothrombin time indicates deficiency of 1 or more factors (I, II, V, VII, or X) or the presence of a coagulation inhibitor. The prothrombin time is also reported as the INR (International Normalized Ratio), based on the ISI (International Sensitivity Index) assigned to the thromboplastin and coagulometer. This assay is used for monitoring "stable" oral anticoagulation. A mixing test of patient and normal plasma (1:2) can be performed, if indicated, to differentiate coagulation factor deficiency from inhibition.

Useful For: Screening to identify a deficiency of 1 or more of the clotting factors of the extrinsic coagulation system (I, II, V, VII, X) due to hereditary deficiency or acquired conditions such as liver disease, vitamin K deficiency, or a specific factor inhibitor Monitoring patients on oral anticoagulant therapy to maintain a patient in a safe therapeutic range

Interpretation: Prolongation of the prothrombin time (PT) can occur as a result of deficiency of 1 or more coagulation factors (acquired or congenital in origin), or the presence of an inhibitor of coagulation such as heparin, a lupus anticoagulant, a "nonspecific" inhibitor such as a monoclonal immunoglobulin, or a specific coagulation factor inhibitor. PT mixing study, using equal volume patient and normal pool plasma, may be performed on specimens with a prolonged PT to assist in differentiating coagulation
factor deficiencies from coagulation inhibitors. Correction of the PT mix to within the normal reference range usually indicates a coagulation factor deficiency (normal plasma in the mixture ensures at least 50% activity of all coagulation factors). If the prolonged PT is due to an inhibitor (eg, specific coagulation factor inhibitor, lupus anticoagulant, heparin), the PT mix typically fails to correct a prolonged PT. However, the presence of a weak inhibitor may be missed by the PT mixing study. Accurate interpretation of both PT and PT mixing study results may often require additional testing. For example, the thrombin time (TT) test is helpful for identifying or excluding the presence of heparin, the platelet neutralization procedure (PNP, using a modified APTT method) for identifying or excluding lupus anticoagulant, the activated partial thromboplastin (APTT) and dilute Russell viper venom time (DRVVT) for further assessment of the common procoagulant pathway, and coagulation factor assays to detect and identify deficient or abnormal factors. These assays are available as components of reflexive and interpretive testing panels in the Special Coagulation Laboratory (eg, PROCT / Prolonged Clot Time Profile).

Reference Values:
Only orderable as part of a coagulation consultation. For more information see 1 of the following:
- LUPPR / Lupus Anticoagulant Profile
- BDIAL / Bleeding Diathesis Profile
- THRMP / Thrombophilia Profile
- PROCT / Prolonged Clot Time Profile

An interpretive report will be provided.


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**Prothrombin Time Mix 1:1**

**Clinical Information:** The prothrombin time (PT) mix is only performed when the PT is abnormally prolonged. Please refer to test PTC / Prothrombin Time (PT), Plasma for an interpretation of results.

**Useful For:** Screening test to detect a deficiency of 1 or more of the clotting factors of the extrinsic coagulation system (I, II, V, VII, X) due to hereditary deficiency or acquired conditions such as liver disease, vitamin K deficiency, or a specific factor inhibitor. Determining the cause of a prolonged PT, factor deficiency versus factor inhibitor

**Interpretation:** Prolongation of the prothrombin time (PT) can occur as a result of deficiency of 1 or more coagulation factors (acquired or congenital in origin), or the presence of an inhibitor of coagulation such as heparin, a lupus anticoagulant, a "nonspecific" inhibitor such as a monoclonal immunoglobulin, or a specific coagulation factor inhibitor. PT mixing study, using equal volume patient and normal pool plasma, may be performed on specimens with a prolonged PT to assist in differentiating coagulation factor deficiencies from coagulation inhibitors. Correction of the PT mix to within the normal reference range usually indicates a coagulation factor deficiency (normal plasma in the mixture ensures at least 50% activity of all coagulation factors). If the prolonged PT is due to an inhibitor (specific coagulation factor inhibitor, lupus anticoagulant, heparin, etc.), the PT mix typically fails to correct a prolonged PT. However, the presence of a weak inhibitor may be missed by the PT mixing study. Accurate interpretation of both PT and PT mixing study results may often require additional testing. For example, the thrombin time (TT) test is helpful for identifying or excluding the presence of heparin, the platelet neutralization procedure (PNP, using a modified APTT method) for identifying or excluding lupus anticoagulant, the activated partial thromboplastin (APTT) and dilute Russell's viper venom time (DRVVT) for further assessment of the common procoagulant pathway, and coagulation factor assays to detect and identify deficient or abnormal factors. These assays are available as components of reflexive and interpretive testing panels in the Special Coagulation Laboratory (eg, PROCT / Prolonged Clot Time Profile).

**Reference Values:**
Only orderable as part of a coagulation consultation. For more information see 1 of the following:
PTTP
40934

Prothrombin Time, Plasma

Clinical Information: Prothrombin is a plasma protein with a molecular weight of 68,700. It is an unstable protein that can split easily into smaller compounds, one of which is thrombin. Prothrombin is formed continually by the liver, and it is continually being used throughout the body for blood clotting. If the liver fails to produce prothrombin, in a day or so prothrombin concentration in the plasma falls too low to provide normal blood coagulation. Vitamin K is required by the liver for normal activation of prothrombin, as well as other clotting factors. Therefore, either lack of vitamin K or the presence of liver disease that prevents normal prothrombin formation can decrease the prothrombin concentration so low that a bleeding tendency results. The prothrombin time (PT) is used as a screening test to detect a deficiency of one or more of the clotting factors of the extrinsic coagulation system (I, II, V, VII, or X) due to a hereditary or acquired deficiency, liver disease, vitamin K deficiency, or presence of inhibitors. Inhibitors include specific coagulation factor inhibitors, Lupus-like anticoagulant inhibitors (eg, antiphospholipid antibodies), and nonspecific prothrombin time inhibitors (eg, monoclonal immunoglobulins, elevated fibrin degradation products). Mixing studies with normal plasma are useful in initial evaluation of prolonged PT when the cause is unknown (eg, not attributable to known oral anticoagulant or known coagulation factor deficiency). One of the following tests may be appropriate, depending on the clinical picture: -LUPPR / Lupus Anticoagulant Profile -THRMP / Thrombophilia Profile -BDIAL / Bleeding Diathesis Profile, Limited -PROCT / Prolonged Clot Time Profile The PT results produced by different assays may vary significantly as there are differences in activity of the tissue factor and the instrument used to perform the test. Tissue factor is isolated from a variety of sources by assay manufacturers, and different batches may have different activity. Calculation of the international normalized ratio (INR) addresses this problem by normalizing the PT result. For this reason, INR is used to monitor oral anticoagulant therapy (warfarin or Coumadin). Warfarin inhibits the enzyme, vitamin K epoxide reductase complex 1 (VKOR c1), responsible for converting vitamin K to its active, reduced form. By inhibiting VKOR c1, warfarin decreases the available active form of vitamin K in the tissues. Thus, when warfarin is given to a patient, the amounts of active prothrombin and factors VII, IX, and X, all formed by the liver degrade and are replaced by inactive factors. Although the coagulation factors continue to be produced, they have greatly decreased coagulant activity. Bleeding is the primary adverse reaction associated with warfarin use, and is among the top 10 drugs with the largest number of serious adverse events reported to the FDA. For these reasons, monitoring therapy closely and adjusting dose accordingly is critical. The international sensitivity index (ISI) is an experimentally derived measurement, usually provided by the thromboplastin manufacturer, reflecting thromboplastin (and PT) sensitivity to coagulation deficiencies. More sensitive thromboplastins have a low ISI (1.0-1.2), whereas less sensitive thromboplastins have a higher ISI (eg, 2.0-3.0). Calculation of the INR is as follows:

\[
\text{INR} = \frac{\text{Patient's PT}}{\text{mean PT of reference range}} \times \text{ISI}
\]

where: -INR=international normalized ratio -ISI=international sensitivity index

Useful For: Screening assay to detect deficiencies of one or more coagulation factors (factors I, II, V, VII, X) Screening assay to detect coagulation inhibition Monitoring intensity of oral anticoagulant therapy when combined with INR reporting

Interpretation: Prothrombin time (PT) may be prolonged due to deficiencies of factors X, VII, V, and II of the extrinsic pathway, presence of inhibitors, or oral anticoagulation therapy. INR therapeutic ranges for orally administered drugs: -Standard-intensity warfarin therapeutic range: 2.0 to 3.0 -High-intensity warfarin therapeutic range: 2.5 to 3.5 Note: The INR should only be used for patients on stable oral
anticoagulant therapy, though it is reported for all patients despite whether they are receiving oral anticoagulants.

**Reference Values:**

**PROTHROMBIN TIME**

9.4-12.5 seconds

**INTERNATIONAL NORMALIZED RATIO (INR)**

0.9-1.1

Standard intensity warfarin therapeutic range: 2.0-3.0
High intensity warfarin therapeutic range: 2.5-3.5

**Clinical References:**

### Protoporphyrins, Fractionation, Washed Erythrocytes

**Clinical Information:** The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrias and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. Testing protoporphyrin fractions is most informative for patients with a clinical suspicion of erythropoietic porphyrinia (EPP) or X-linked dominant protoporphyrinia (XLDP). Clinical presentation of EPP and XLDP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Although genetic in nature, environmental factors exacerbate symptoms, significantly impacting the severity and course of disease. EPP is caused by diminished ferrochelatase activity resulting in significantly increased free protoporphyrin levels in erythrocytes, plasma, and feces. X-linked dominant protoporphyrinia is caused by gain-of-function mutations in the C-terminal end of ALAS2 gene and results in elevated erythrocyte levels of free and zinc-complexed protoporphyrin, and total protoporphyrin in plasma and feces. Other possible cases of elevated erythrocyte zinc-complexed protoporphyrin may include: -Iron-deficiency anemia, the most common cause -Chronic intoxication by heavy metals (primarily lead) or various organic chemicals -Congenital erythropoietic porphyria (CEP), a rare autosomal recessive porphyria caused by deficient uroporphyrinogen III synthase -Hepatoerythropoietic porphyrinia (HEP), a rare autosomal recessive porphyria caused by deficient uroporphyrinogen decarboxylase Typically, the workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyrinia (Auto) Testing Algorithm and Porphyrinia (Cutaneous) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies. There are 2 test options: PPFE / Protoporphyrins, Fractionation, Whole Blood and PPFWE / Protoporphyrins, Fractionation, Washed Erythrocytes. The whole blood option is easiest for clients but requires that the specimen arrive at Mayo Medical Laboratories within 7 days of draw. When this cannot be ensured, washed frozen erythrocytes, which are stable for 14 days, should be submitted.

**Useful For:** Preferred test for analysis of erythrocyte protoporphyrin fractions Preferred test for evaluating patients with possible diagnoses of erythropoietic protoporphyrinia and X-linked dominant protoporphyrinia Establishing a biochemical diagnosis of erythropoietic protoporphyrinia, and X-linked dominant protoporphyrinia

**Interpretation:** Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and available.
Reference Values:
FREE PROTOPORPHYRIN  
<20 mcg/dL packed cells

ZINC-COMPLEXED PROTOPORPHYRIN  
<60 mcg/dL packed cells


PPFE

Protoporphyrins, Fractionation, Whole Blood

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Depending on the specific enzyme involved, various porphyrins and their precursors accumulate in different specimen types. The patterns of porphyrin accumulation in erythrocytes and plasma and excretion of the heme precursors in urine and feces allow for the detection and differentiation of the porphyrias. Testing protoporphyrin fractions is most informative for patients with a clinical suspicion of erythropoietic protoporphyria (EPP) or X-linked dominant protoporphyria (XLDPP). Clinical presentation of EPP and XLDPP is identical with onset of symptoms typically occurring in childhood. Cutaneous photosensitivity in sun-exposed areas of the skin generally worsens in the spring and summer months. Common symptoms may include itching, edema, erythema, stinging or burning sensations, and occasionally scarring of the skin in sun-exposed areas. Although genetic in nature, environmental factors exacerbate symptoms, significantly impacting the severity and course of disease. EPP is caused by diminished ferrochelatase activity resulting in significantly increased free protoporphyrin levels in erythrocytes, plasma, and feces. X-linked dominant protoporphyria is caused by gain-of-function mutations in the C-terminal end of ALAS2 gene and results in elevated erythrocyte levels of free and zinc-complexed protoporphyrin in erythrocytes, and total protoporphyrin levels in plasma and feces. Other possible causes of elevated erythrocyte zinc-complexed protoporphyrin may include: -Iron-deficiency anemia, the most common cause -Chronic intoxication by heavy metals (primarily lead) or various organic chemicals -Congenital erythropoietic porphyria (CEP), a rare autosomal recessive porphyria caused by deficient uroporphyrinogen III synthase -Hepatoerythropoietic porphyria (HEP), a rare autosomal recessive porphyria caused by deficient uroporphyrinogen decarboxylase Typically, the workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Acute) Testing Algorithm and Porphyria (Cutaneous) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies. There are 2 test options: PPFE / Protoporphyrins, Fractionation, Whole Blood and PPFWE / Protoporphyrins, Fractionation, Washed Erythrocytes. The whole blood option is easiest for clients but requires that the specimen arrive at Mayo Medical Laboratories within 7 days of draw. When this cannot be ensured, washed frozen erythrocytes, which are stable for 14 days, should be submitted.

Useful For: Evaluating patients with possible diagnoses of erythropoietic protoporphyria or X-linked dominant protoporphyria Establishing a biochemical diagnosis of erythropoietic protoporphyria and X-linked dominant protoporphyria

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, and recommendations for additional testing when indicated and
available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

FREE PROTOPORPHYRIN

<20 mcg/dL packed cells

ZINC-COMPLEXED PROTOPORPHYRIN

<60 mcg/dL packed cells

**Clinical References:**


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**PROTR 9797**

**Protriptyline (Vivactyl)**

**Reference Values:**

Reference Range: 50 - 170 ng/mL

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**PRSSZ 35532**

**PRSS1 Gene, Full Gene Analysis**

**Clinical Information:**

Hereditary pancreatitis (HP) is a rare autosomal dominant disorder associated with approximately 80% penetrance. HP is characterized by early onset acute pancreatitis during childhood or early adolescence. The acute pancreatitis in these patients generally progresses to chronic pancreatitis by adulthood and can eventually lead to both exocrine and endocrine pancreatic insufficiency. Patients with HP are also at an increased risk for developing pancreatic cancer. Studies have estimated the lifetime risk of developing pancreatic cancer to be as high as 40%. Mutations in the protease serine 1 or cationic trypsinogen (PRSS1) gene are a common cause of HP. It has been reported that as many as 80% of patients with symptomatic hereditary pancreatitis have a causative PRSS1 mutation. HP cannot be clinically distinguished from other forms of pancreatitis. However, PRSS1 mutations are generally restricted to individuals with a family history of pancreatitis. PRSS1 mutations are infrequently found in patients with alcohol-induced and tropical pancreatitis. Although several mutations have been identified, the R122H, N29I and A16V mutations are the most common disease-causing mutations associated with HP. Data suggest that the R122H mutation results in more severe disease and earlier onset of symptoms than the A16V mutation. Although these 3 alterations account for >90% of mutations detected in the cationic trypsinogen gene, the inability to identify mutations in approximately 20% of families with HP suggests the involvement of other loci or unidentified mutations in the cationic trypsinogen gene. Mutations in other genes, such as SPINK1, CFTR and CTRC have been associated with hereditary and familial pancreatitis. Abnormalities in these genes are not detected by this assay. However, genetic testing for these genes simultaneously, including PRSS1, is available by ordering HPPAN / Hereditary Pancreatitis Panel.

**Useful For:** Confirmation of suspected clinical diagnosis of hereditary pancreatitis (HP) in patients with chronic pancreatitis Identification of familial PRSSI mutation to allow for predictive and diagnostic testing in family members

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known,
predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Pseudochoolinesterase, Dibucaine Inhibition, Serum**

**Clinical Information:** Serum cholinesterase, often called pseudochoolinesterase (PCHE), is distinguished from acetylchoolinesterase or "true cholinesterase," by both location and substrate. Acetylchoolinesterase is found in erythrocytes, in the lungs and spleen, in nerve endings, and in the gray matter of the brain. It is responsible for the hydrolysis of acetylcholine released at the nerve endings to mediate transmission of the neural impulse across the synapse. PCHE, the serum enzyme, is also found in liver, pancreas, heart, and white matter. Its biological role is unknown. The organophosphorus-containing insecticides are potent inhibitors of the true cholinesterase and cause depression of PCHE. Low values of PCHE are also found in patients with liver disease. In general, patients with acute hepatitis and chronic hepatitis of long duration will show a 30% to 50% decrease in PCHE values, while patients with advanced cirrhosis and carcinoma with metastases will show a 50% to 70% decrease. Essentially normal values are seen in chronic hepatitis, mild cirrhosis, and obstructive jaundice. PCHE metabolizes the muscle relaxants succinylcholine and mivacurium, and therefore, alterations in PCHE will influence the physiologic effect of these drugs. In normal individuals (approximately 94% of the population) certain drugs and other agents, such as dibucaine and fluoride, will almost completely inhibit the PCHE activity. A small number of patients (<1% of the population) are homozygous for an atypical gene controlling PCHE. These individuals generally have low levels of PCHE which are not inhibited by dibucaine and fluoride, will not hydrolyze the drugs succinylcholine and mivacurium rapidly enough, and may enter a period of prolonged apnea. In addition to fluoride and dibucaine alleles, a "silent gene" has also been identified which shows little or no activity. More recently, the J and K variants also have been identified. All combinations of heterozygotes of the various alleles have been found. This is important because these atypical enzymes will show varying levels of enzyme activity and resistance to dibucaine although the patients clinically show prolonged apnea.

**Useful For:** Identifying patients who are homozygous for the atypical gene, and have low levels of pseudochoolinesterase (PCHE) which are not inhibited by dibucaine Identifying patients who are heterozygous for the atypical gene, have lower than normal levels of PCHE and varying levels of inhibition with dibucaine

**Interpretation:** Patients with normal pseudochoolinesterase (PCHE) activity show 70% to 90% inhibition by dibucaine, while patients homozygous for the abnormal allele show little or no inhibition (0%-20%) and usually low levels of enzyme. Heterozygous patients have intermediate PCHE levels and response to inhibitors. The atypical gene is inherited in an autosomal recessive pattern. In a positive patient, family members should be tested. Several reports have shown that 65% to 75% of patients who respond abnormally to succinylcholine had at least 1 abnormal gene, had low activity due to an acquired deficiency such as liver disease, or had received an inappropriate dose of drug. The remaining 25% to 35% of patients appeared to have the usual or normal genotype but nevertheless displayed long periods of apnea. Although reasons could not be established, it is possible that these cases represent unknown genotypes. Therefore, although many symptomatic patients will show moderate to significant resistance to
dibucaine and low enzyme activity, not all will. In all cases, it is recommended that succinylcholine and mivacurium be avoided, or the dose greatly reduced.

**Reference Values:**

**DIBUTCAINE INHIBITION**
- 70-90%
- Congenital deficiency: 18-20%

**PSEUDOCHOLINESTERASE, TOTAL**
- Males: 3,100-6,500 U/L
- Females
  - 18-49 years: 1,800-6,600 U/L
  - > or =50 years: 2,550-6,800 U/L
- Reference values have not been established for patients that are <18 years of age.

**Clinical References:**

**Pseudochoolinesterase, Total, Serum**

**Clinical Information:** Serum cholinesterase, often called pseudocholinesterase (PCHE), is distinguished from acetylcholinesterase or "true cholinesterase," by both location and substrate. Acetylcholinesterase is found in erythrocytes, in the lungs and spleen, in nerve endings, and in the gray matter of the brain. It is responsible for the hydrolysis of acetylcholine released at the nerve endings to mediate transmission of the neural impulse across the synapse. PCHE, the serum enzyme, is also found in liver, pancreas, heart, and white matter. Its biological role is unknown. The organophosphorus-containing insecticides are potent inhibitors of the true cholinesterase and also cause depression of PCHE. Low values of PCHE are also found in patients with liver disease. In general, patients with advanced cirrhosis and carcinoma with metastases will show a 50% to 70% decrease. Essentially normal values are seen in chronic hepatitis, mild cirrhosis, and obstructive jaundice. PCHE metabolizes the muscle relaxants succinylcholine and mivacurium, and therefore, alterations in PCHE will influence the physiologic effect of these drugs. In normal individuals (approximately 94% of the population) certain drugs and other agents, such as dibucaine and fluoride, will almost completely inhibit the PCHE activity. A small number of individuals (<1% of the population) have been shown to have genetic variants of the enzyme, and cannot metabolize the muscle relaxants succinylcholine and mivacurium and experience prolonged apnea. These individuals generally have low levels of PCHE, which is not inhibited by dibucaine or fluoride. These individuals are either homozygotes or compound heterozygotes for an atypical gene(s) controlling PCHE. Simple heterozygotes have also been identified who show intermediate enzyme values and inhibition.

**Useful For:** Monitoring exposure to organophosphorus insecticides Monitoring patients with liver disease, particularly those undergoing liver transplantation Identifying patients who are homozygous or heterozygous for an atypical gene and have low levels of pseudocholinesterase

**Interpretation:** Patients with normal pseudocholinesterase (PCHE) activity show 70% to 90% inhibition by dibucaine, while patients homozygous for the abnormal allele show little or no inhibition (0%-20%) and usually low levels of enzyme. Heterozygous patients have intermediate PCHE levels and response to inhibitors. The atypical gene is inherited in an autosomal recessive pattern. In a positive patient, family members should be tested. Decreasing or low levels may indicate exposure to organophosphorus insecticides, as long as liver disease and an abnormal allele have been ruled out.

**Reference Values:**
- Males
> or =18 years: 3,100-6,500 U/L

Females
18-49 years: 1,800-6,600 U/L
> or =50 years: 2,550-6,800 U/L

Reference values have not been established for patients that are <18 years of age.

**Clinical References:**

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**Psychosine, Blood**

**Clinical Information:** Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive lysosomal storage disorder caused by an enzyme deficiency of galactocerebrosidase (GALC). GALC facilitates the lysosomal degradation of psychosine (galactosylsphingosine) and 3 other substrates (galactosylceramide, lactosylceramide, and lactosylsphingosine). Krabbe disease is caused by mutations in the GALC gene, and it has an estimated frequency of 1 in 100,000 births. Eighty-five percent to 90% of patients present before the first year of life with central nervous system impairment including increasing irritability, developmental delay, and sensitivity to stimuli. Rapid neurodegeneration including white matter disease follows, with death usually occurring by age 2. Ten percent to 15% of individuals have late onset forms of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression, presenting anytime from age 6 months to the seventh decade of life. The clinical course of Krabbe disease can be variable, even within the same family. Newborn screening for Krabbe disease has recently been implemented in some states. The early (presymptomatic) identification and subsequent testing of infants at risk for Krabbe disease may be helpful in reducing the morbidity and mortality associated with this disease. While treatment is mostly supportive, hematopoietic stem cell transplantation has shown some success if performed prior to onset of neurologic damage. Psychosine (PSY) is a neurotoxin at elevated concentrations. Importantly, it is 1 of 4 substrates degraded by galactocerebrosidase. It has been shown to be elevated in patients with active Krabbe disease or with Saposin A cofactor deficiency, and therefore, may be a useful biomarker for the presence of disease or disease progression. Reduced or absent galactocerebrosidase in leukocytes (CBGC / Galactocerebrosidase, Leukocytes) or dried blood spots (PLSD / Lysosomal and Peroxisomal Storage Disorders Screen, Blood Spot) along with psychosine analysis can indicate a diagnosis of Krabbe disease. Molecular sequencing of the GALC gene (KRABZ / Krabbe Disease, Full Gene Analysis and Large [30 kb] Deletion, PCR) allows for detection of the disease-causing mutations in affected patients and carrier detection in family members. Individuals with a disease phenotype similar to Krabbe disease, but with normal GALC activity, may have Saposin A cofactor deficiency. Saposin A cofactor deficiency also results in elevated psychosine levels. Testing for this condition via molecular analysis of PSAP is useful in those with elevated psychosine but normal GALC activity.

**Useful For:** Aids in the biochemical diagnosis of Krabbe disease Follow-up of individuals affected with Krabbe disease Follow-up testing after an abnormal newborn screening result for Krabbe disease

**Interpretation:** An interpretive report is provided. An elevation of psychosine is indicative of symptomatic Krabbe disease or symptomatic Saposin A cofactor deficiency.

**Reference Values:**
Normal <3.0 nmol/L psychosine

**Clinical References:**
4. Turgeon CT, Orsini JJ, Sanders KA, et al: Measurement of psychosine in dried blood spots—a possible improvement to newborn screening programs for Krabbe disease
PSY
62235

**Psychosine, Blood Spot**

**Clinical Information:** Krabbe disease (globoid cell leukodystrophy) is an autosomal recessive lysosomal storage disorder caused by an enzyme deficiency of galactocerebrosidase (GALC). GALC facilitates the lysosomal degradation of psychosine (galactosylsphingosine) and 3 other substrates (galactosylceramide, lactosylceramide and lactosylsphingosine). Krabbe disease is caused by mutations in the GALC gene, and it has an estimated frequency of 1 in 100,000 births. Eighty-five percent to 90% of patients present before the first year of life with central nervous system impairment including increasing irritability, developmental delay, and sensitivity to stimuli. Rapid neurodegeneration including white matter disease follows with death usually occurring by age 2. Ten percent to 15% of individuals have late onset forms of the disease that are characterized by ataxia, vision loss, weakness, and psychomotor regression presenting anytime from age 6 months to the seventh decade of life. The clinical course of Krabbe disease can be variable, even within the same family. Newborn screening for Krabbe disease has recently been implemented in some states. The early (presymptomatic) identification and subsequent testing of infants at risk for Krabbe disease may be helpful in reducing the morbidity and mortality associated with this disease. While treatment is mostly supportive, hematopoietic stem cell transplantation has shown some success if performed prior to onset of neurologic damage. Psychosine (PSY) is a neurotoxin at elevated concentrations. Importantly, it is 1 of 4 substrates degraded by galactocerebrosidase. It has been shown to be elevated in patients with active Krabbe disease or with Saposin A cofactor deficiency and, therefore, may be a useful biomarker for the presence of disease or disease progression. Reduced or absent galactocerebrosidase in leukocytes (CBGC / Galactocerebrosidase, Leukocytes) or dried blood spots (PLSD / Lysosomal and Peroxisomal Storage Disorders Screen, Blood Spot) along with psychosine analysis can indicate a diagnosis of Krabbe disease. Molecular sequencing of the GALC gene (KRABZ / Krabbe Disease, Full Gene Analysis and Large [30 kb] Deletion, PCR) allows for detection of the disease-causing mutations in affected patients and carrier detection in family members. Individuals with a disease phenotype similar to Krabbe disease, but with normal GALC activity, may have Saposin A cofactor deficiency. Saposin A cofactor deficiency also results in elevated psychosine levels. Testing for this condition via molecular analysis of PSAP is useful in those with elevated psychosine but normal GALC activity.

**Useful For:** Aids in the biochemical diagnosis of Krabbe disease and Saposin A cofactor deficiency  
Follow-up of individuals affected with Krabbe disease Follow-up testing after an abnormal newborn screening result for Krabbe disease

**Interpretation:** An interpretive report is provided. An elevation of psychosine is indicative of symptomatic Krabbe disease or symptomatic Saposin A cofactor deficiency.

**Reference Values:**  
Normal <3 nmol/L psychosine

**Clinical References:**  
Clinical Information: Germline mutations in the PTEN gene are associated with a rare collection of clinical syndromes referred to as PTEN hamartoma tumor syndrome (PHTS). This includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus syndrome (PS) and Proteus-like syndrome (PLS). Although each of these syndromes has its own unique features, all 4 appear to be associated with multiple hamartomatous lesions, vascular lesions, and macrocephaly. Affected individuals have an increased risk of cancer, including cancers of the breast, endometrium, thyroid, colon, and kidney. PHTS is an autosomal dominant disorder and penetrance is believed to be quite high. CS is a multiple hamartoma syndrome associated with trichilemmomas, mucocutaneous papillomatous papules, and macrocephaly. Affected individuals are at an increased risk for breast, thyroid, and endometrial carcinoma. BRRS is characterized by macrocephaly, intestinal hamartomas, lipomatosis, hemangiomas, and pigmented macules on the glans penis. PS is associated with congenital malformations, overgrowth, macrocephaly, hyperostosis, connective tissue nevi, and epidermal nevi. PLS refers to individuals who have features of PS, but do not meet diagnostic criteria.

Useful For: Confirming a diagnosis of PTEN hamartoma tumor syndrome, which includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome, or Proteus-like syndrome

Identifying mutations in the PTEN gene

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics (ACMG) recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.


FPTH 91504

PTH Accuratio Comprehensive Profile

Reference Values:
COMPREHENSIVE PROFILE

TOTAL PTH Reference Range: 14.0 - 66.0 pg/mL
CAP PTH Reference Range: 5.0 - 39.0 pg/mL
CIP VALUE Reference Range: 2.5 - 29.0 pg/mL
CAP/CIP Reference Range: 1.1 - 6.9 ratio

Low ratio or PTH values are associated with Adynamic bone turnover status for an ESRD patient.

Total PTH:
Total Intact PTH is the sum of CAP PTH and N-truncated PTH fragment (likely 7-84) Total PTH = Intact PTH = CAP + CIP.
FDA approved.

CAP PTH:
CAP stands for Cyclase Activating PTH and is the same as Whole PTH which is 1-84 PTH and which raises bone turnover.
FDA approved.

**CIP VALUE:**
CIP stands for Cyclase Inactive PTH and the N-truncated PTH fragment, likely 7-84 PTH. CIP = Total PTH â€“ CAP.

**CAP/CIP:**
CAP/CIP ratio is a calculated value and has been shown to be 93% predictive of bone turnover for the ESRD patient, however, bone biopsy is 100% predictive, therefore, clinical correlation is recommended.

Reference ranges were established using a 95% reference interval on a normal population with normal functioning kidneys. These reference ranges should not be applied to ESRD patients with impaired or non-functioning renal function.


**FPTH 90182**
**PTH Antibody**
**Reference Values:**
Negative

**PU1 70545**
**PU.1 Immunostain, Technical Component Only**

**Clinical Information:** PU.1 is an erythroblast transformation specific (ETS) family transcription factor that regulates expression of immunoglobulin genes and other genes important in B-cell development. The nuclear protein is expressed in B cells in the germinal center and mantle zone. It is not expressed in plasma cells. PU.1 also plays a role in the differentiation of myeloid cells and is expressed in macrophages (strong staining), mast cells, early erythroid cells, and megakaryocytes. Expression of BOB.1, OCT-2, and PU.1 transcription factors are often downregulated in classical Hodgkin lymphoma. This property can be useful in lymphoma diagnosis.

**Useful For:** Classification of lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

PU.1 putative binding sites in the BCL-6 promotor. J Pathol 2005 Jul;206(3):312-319

Pumpkin Seed, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<tr>
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<td>3.50-17.4</td>
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<tr>
<td>4</td>
<td>17.5-49.9</td>
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</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
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</tbody>
</table>


Purines and Pyrimidines Panel, Plasma
**Clinical Information:** Purines (adenine, guanine, xanthine, hypoxanthine, uric acid) and pyrimidines (uracil, thymine, cytosine, orotic acid) are involved in all biological processes, providing the basis for storage, transcription, and translation of genetic information as RNA and DNA. Purines are required by all cells for growth and survival and also play a role in signal transduction and translation. Purines and pyrimidines originate primarily from endogenous synthesis, with dietary sources playing only a minor role. The end product of purine metabolism is uric acid (2,6,8-trioxypurine), which must be excreted continuously to avoid toxic accumulation. Disorders of purine and pyrimidine metabolism can involve all organ systems at any age. The diagnosis of the specific disorders of purine and pyrimidine metabolism is based upon the clinical presentation of the patient, determination of specific concentration patterns of purine and pyrimidine metabolites, and confirmatory enzyme assays and molecular genetic testing. Over 35 inborn errors of purine and pyrimidine metabolism have been documented. Clinical features are dependent upon the specific disorder, but represent a broad spectrum of clinical manifestations that may include immunodeficiency, developmental delay, nephropathy, and neurologic involvement. The most commonly described disorder involves a deficiency of hypoxanthine phosphoribosyl transferase (HPRT), the majority of which have classic Lesch-Nyhan syndrome. Lesch-Nyhan syndrome was described in 1964 as the first disorder of purine metabolism. It is an X-linked disorder characterized by severe neurologic impairment, the development of a compulsive self-destructive behavior, and uric acid nephropathy. Treatments that can mitigate the potentially devastating effects of these diseases are disorder dependent, therefore, early recognition through screening and subsequent confirmatory testing is highly desirable.

**Useful For:** Evaluating patients with symptoms suspicious for disorders of purine and pyrimidine metabolism Monitoring patients with disorders of purine and pyrimidine metabolism Laboratory evaluation of primary and secondary hyperuricemias

**Interpretation:** Abnormal concentrations of measurable compounds will be reported along with an interpretation. The interpretation of an abnormal metabolite pattern includes an overview of the results and of their significance, a correlation to available clinical information, possible differential diagnosis, recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis), name, and phone number of contacts who may provide these studies at the Mayo Clinic or elsewhere, and a phone number of the laboratory directors in case the referring physician has additional questions.

**Reference Values:**

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<th>Compounds</th>
<th>0-1 years</th>
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<th>5-18 years</th>
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Current as of October 11, 2018 2:20 pm CDT   800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com

PUPYU 41977

Purines and Pyrimidines Panel, Urine

Clinical Information: Purines (adenine, guanine, xanthine, hypoxanthine) and pyrimidines (uracil, thymine, cytosine, orotic acid) are involved in all biological processes, providing the basis for storage, transcription, and translation of genetic information as RNA and DNA. Purines are required by all cells for growth and survival and also play a role in signal transduction and translation. Purines and pyrimidines originate primarily from endogenous synthesis, with dietary sources playing only a minor role. The end product of purine metabolism is uric acid (2,6,8-trioxypurine), which must be excreted continuously to avoid toxic accumulation. Numerous inborn errors of purine and pyrimidine metabolism have been documented. Clinical features are dependent upon the specific disorder, but represent a broad spectrum of manifestations that may include immunodeficiency, developmental delay, nephropathy, and neurologic involvement. The most commonly described disorder involves a deficiency of hypoxanthine phosphoribosyl transferase (HPRT) which causes 3 overlapping clinical syndromes depending on the amount of residual enzyme activity. The majority of patients with HPRT deficiency have classic Lesch-Nyhan syndrome, a severe disorder, described in 1964 as the first disorder of purine metabolism. It is an X-linked disorder characterized by severe neurologic impairment, severe to moderate cognitive impairment, the development of a compulsive self-destructive behavior, and uric acid nephropathy. Treatment is mainly supportive and includes the use of special devices to prevent self-injury. Disorders of purine and pyrimidine metabolism can involve all organ systems at any age. The diagnosis of the specific disorders of purine and pyrimidine metabolism is based upon the clinical presentation of the patient, determination of specific concentration patterns of purine and pyrimidine metabolites, and confirmatory enzyme assays and/or molecular genetic testing.

Useful For: Evaluating patients with symptoms suspicious for disorders of purine and pyrimidine metabolism Monitoring patients with disorders of purine and pyrimidine metabolism Laboratory evaluation of primary and secondary hyperuricemias

Interpretation: Abnormal concentrations of measurable compounds will be reported along with an interpretation. The interpretation of an abnormal metabolite pattern includes an overview of the results and of their significance, a correlation to available clinical information, possible differential diagnosis, recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis), name, and phone number of contacts who may provide these studies at the Mayo Clinic or elsewhere, and a phone number of the laboratory directors in case the referring physician has additional questions.

Reference Values:

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<th>Metabolite</th>
<th>0-3 Years</th>
<th>4-6 Years</th>
<th>7-12 Years</th>
<th>13-18 Years</th>
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Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
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<th>Substance</th>
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**Clinical References:**

**FPYRE 57540**

**Pyrethrum IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

**FPYD 90281**

**Pyridostigmine, Serum/Plasma**

**Reference Values:**
Reporting limit determined each analysis

Synonym(s): Mestinon

30-125 ng/mL plasma in myasthenia gravis patients restores normal neuronal transmission.
Specimens must be kept frozen.

**Pyridoxal 5-phosphate (CSF)**

**Reference Values:**
- 30-80 nmol/L 0 to <3 months
- 23-65 nmol/L 3 months to <1 years
- 15-51 nmol/L 1 year to <4 years
- 23-65 nmol/L 4 years to adult

**Pyridoxal 5-Phosphate (PLP), Plasma**

**Clinical Information:** Vitamin B6 is a complex of 6 vitamers: pyridoxal, pyridoxol, pyridoxamine, and their 5'-phosphate esters. Due to its role as a cofactor in a number of enzymatic reactions, pyridoxal phosphate (PLP) has been determined to be the biologically active form of vitamin B6. Vitamin B6 deficiency is a potential cause of burning mouth syndrome and a possible potentiating factor for carpal tunnel and tarsal tunnel syndromes. Persons who present chronic, progressive nerve compression disorders may be deficient in vitamin B6 and should be evaluated. Vitamin B6 deficiency is associated with symptoms of scaling of the skin, severe gingivitis, irritability, weakness, depression, dizziness, peripheral neuropathy, and seizures. In the pediatric population, deficiencies have been characterized by diarrhea, anemia, and seizures. Markedly elevated PLP in conjunction with low levels of pyridoxic acid are observed in cases of hypophosphatasia, a disorder characterized by low levels of alkaline phosphatase and a range of skeletal abnormalities.

**Useful For:** Determining vitamin B6 status, including in persons who present with progressive nerve compression disorders, such as carpal tunnel and tarsal tunnel syndromes Determining the overall success of a vitamin B6 supplementation program Diagnosis and evaluation of hypophosphatasia

**Interpretation:** Levels for fasting individuals falling in the range of 3 to 30 mcg/L for pyridoxic acid (PA) and 5 to 100 mcg/L for pyridoxal 5-phosphate (PLP) are indicative of adequate nutrition. The following are interpretative guidelines based upon PLP and PA results: If PLP is >100 mcg/L; or -If PLP is >100 mcg/L and PA is < 30, the increased pyridoxal 5-phosphate is suggestive of hypophosphatasia. Consider analysis of serum alkaline phosphatase isoenzymes (ALK1 / Alkaline Phosphatase, Total and Isoenzymes, Serum) and urinary phosphoethanolamine (AAPD / Amino Acids, Quantitative, Random, Urine). -If PLP is >100 mcg/L and PA is 31 to 100 mcg/L; or PLP is 81 to 100 mcg/L and PA is < or =30 mcg/L, the increased pyridoxal 5-phosphate is likely related to dietary supplementation; however a mild expression of hypophosphatasia cannot be excluded. Consider analysis of serum alkaline phosphatase isoenzymes (ALK1 / Alkaline Phosphatase, Total and Isoenzymes, Serum) and urinary phosphoethanolamine (AAPD / Amino Acids, Quantitative, Random, Urine). -If PLP is 51 to 80 mcg/L or PLP is 81 to 100 mcg/L and PA is >30; or PLP is >100 mcg/L and PA is >100 mcg/L, the elevated pyridoxal 5-phosphate is likely due to dietary supplementation.

**Reference Values:**
- 5-50 mcg/L

**Clinical References:**
**Pyrimidine 5' Nucleotidase, Blood**

**Clinical Information:** Pyrimidine 5' nucleotidase (P5’NT) is involved in the catabolism of RNA, which is a normal constituent of reticulocytes but not of mature erythrocytes. A deficiency of P5’NT (also called uridine 5' monophosphate hydrolase) is a cause of congenital non-spherocytic hemolytic anemia (OMIM #266120) and is associated with a persistent reticulocytosis. Deficiency of P5’NT is caused by homozygous or compound heterozygous mutations of the NT5C3A gene at chromosome 7p14 and results in the abnormal accumulation of pyrimidine nucleotides. The disorder is classically associated with basophilic stippling of the red blood cells. Assaying for the presence of pyrimidine nucleotides serves as a surrogate marker for P5’NT deficiency, as the enzymatic assay is difficult.

**Useful For:** Evaluation of persistent reticulocytosis and marked basophilic stippling Evaluation of hemolytic anemia

**Interpretation:** A normal result indicates the absence of pyrimidine nucleotides and indicates normal P5’NT function. An abnormal result (abnormal spectral scan) indicates the presence of pyrimidine nucleotides and likely P5’NT deficiency. Lead poisoning can also inhibit P5NT function. If this is suspected, correlation with blood lead levels is recommended.

**Reference Values:**
Normal

**Clinical References:**

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**Pyruvate Dehydrogenase Complex (PDHC), Fibroblasts**

**Clinical Information:** The pyruvate dehydrogenase complex (PDHC) catalyzes the oxidative decarboxylation of pyruvate to acetyl-CoA, a critical step in the production of cellular energy. PDHC is a multienzyme complex located in the inner mitochondrial membrane, consisting of 6 different components: pyruvate decarboxylase (E1, with alpha and beta subunits), dihydrolipoic transacetylase (E2), dihydrolipoyl dehydrogenase (E3), 2 regulatory enzymes (PDH kinase and PDH phosphatase), and E3-binding protein. PDHC deficiency is a mitochondrial disorder with a variable clinical presentation ranging from fatal congenital lactic acidosis to relatively mild ataxia or neuropathy. In infants and children with PDHC deficiency, the most common features are delayed development and hypotonia, as well as acquired microcephaly. Seizures and ataxia are also frequent features. Less common manifestations include congenital brain malformations, particularly ventriculomegaly and agenesis of the corpus callosum, or degenerative changes, including Leigh disease. Facial dysmorphism is seen in a small portion of patients. PDHC deficiency is one of the most common causes of primary lactic acidosis in children. The severity of the disease progression is thought to be related to the severity of the lactic acidosis as well as the level of residual enzyme activity. PDHC deficiency can be caused by defects in the E1 alpha, E1 beta, E2, or E3 subunits. The most common cause of PDHC deficiency is a defect in the E1 alpha gene, located on the X chromosome. Both females and males with an E1 alpha gene mutation are affected with PDHC deficiency, thus it is classified as X-linked dominant. Mutations in the E1 alpha gene are typically de novo. The most important initial diagnostic test is the measurement of blood and cerebrospinal fluid lactate and pyruvate, along with a lactate-to-pyruvate (L:P) ratio (typically normal ratio with elevated lactate and pyruvate). Additionally, plasma amino acids (AAQP / Amino Acids, Quantitative, Plasma) may detect an increase in alanine. A diagnosis of PDHC deficiency depends on the measurement of enzyme activity in cells or tissues, most commonly in skin fibroblasts.

**Useful For:** Evaluation of patients with a clinical suspicion of a pyruvate dehydrogenase complex deficiency or an energy metabolism disorder

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**Interpretation:** When below-normal enzyme activities are detected, a detailed interpretation is given. This interpretation includes an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional biochemical testing.

**Reference Values:**
- >25.00 nmol/min/g protein (Normal)
- 5.00-25.00 nmol/min/g protein (Indeterminate)
- <5.00 nmol/min/g protein (Deficient)

Reference values apply to all ages.

**Clinical References:**

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**PKLRG 64564**

**Pyruvate Kinase Liver and Red Blood Cell (PKLR) Full Gene Sequencing and Large Deletion Detection**

**Clinical Information:** The glycolytic pathway is used by all tissues for energy production through the formation of ATP. It is particularly important in red blood cells, which are dependent upon this pathway for energy due to their lack of mitochondria. The PKLR gene encodes for pyruvate kinase, the rate-limiting glycolytic enzyme that catalyzes the transphosphorylation from phosphoenolpyruvate (PEP) to adenosine diphosphate (ADP) creating pyruvate and adenosine triphosphate (ATP). Pyruvate kinase (PK) deficiency is a relatively common cause of hereditary nonspherocytic hemolytic anemia, with an estimated prevalence of 1:20,000 among people of European descent. The severity of hemolysis varies from fully compensated forms to life-threatening neonatal anemia requiring transfusions. Over 200 different variants have been reported in the PKLR gene. Most are single nucleotide substitutions although rarer large deletions have also been identified. Pyruvate kinase deficiency is inherited in an autosomal recessive manner and genetic results should be correlated with enzyme levels performed remote from transfusion when possible. Pyruvate kinase deficiency can be difficult to interpret based on enzyme level alone and may be only mildly decreased or normal in those with the most severe symptoms or after splenectomy due to reticulocytosis. Comparison to other RBC enzyme levels is usually very helpful in this regard. Heterozygous carriers of PKLR variants have intermediate enzyme levels and are not symptomatic.

**Useful For:** Aid in the diagnosis of pyruvate kinase (PK) deficiency, Ascertain a causative variant in the PKLR gene of patients with low or relatively low levels of erythrocytic PK enzymatic activity, Ascertain carrier status of family members of individuals diagnosed with PK deficiency for genetic counseling purposes

**Interpretation:** All detected alterations will be evaluated according to current ACMG recommendations. Variants will be classified based on known, predicted, or possible effect on gene pathogenicity and reported with interpretive comments detailing their potential or known clinical significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
1. OMIN 609712 Pyruvate Kinase, Liver and Red Blood Cell; PKLR. Accessed November 2016. Available at OMIM.org

**Pyruvate Kinase, Erythrocytes**

**Clinical Information:** Deficiencies of most of the enzymes of the Embden-Meyerhof (glycolytic) pathway, including pyruvate kinase (PK), have been reported. PK deficiency, although relatively rare, is the erythrocyte enzyme deficiency most frequently found to be a cause of chronic nonspherocytic hemolytic anemia (CNSHA). It is an autosomal recessive disorder and parents of affected patients are typically carriers. It is possible the mutation arose as partial protection against malaria. PK deficiency is the most easily masked of the RBC enzyme disorders and is therefore difficult to classify without complete information which may require correlation with results of PKLR gene molecular testing (PKLRG / Pyruvate Kinase Liver and Red Blood Cell (PKLR) Full Gene Sequencing and Large Deletion Detection). Most hemolytic anemias due to PK deficiency are associated with activity levels less than 40% of mean normal. However, some patients with clinically significant hemolysis can have normal or only mildly decreased PK enzyme activity, which paradoxically may occur in individuals with the most severe symptoms. Carriers (heterozygotes) may show mildly decreased activity and are hematologically normal. Some PK carrier states can exacerbate other RBC disorders (ie coincident glucose-6-phosphate dehydrogenase: G6PD deficiency or hemoglobin S trait). Clinically significant PK deficiency manifests in widely variable severity ranging from incidental compensated mild normocytic anemia to severe neonatal anemia. Other symptoms include jaundice, early gallstones, splenomegaly and iron overload even in the absence of frequent transfusions. Rare severe forms are associated with hydrops fetalis/fetal demise. Rarely, acquired PK deficiency can arise secondary to myeloid neoplasms.

**Useful For:** Evaluation of nonspherocytic hemolytic anemia Evaluation of neonatal anemia Evaluation of unusually severe hemoglobin S trait Evaluation of unusually severe glucose-6-phosphate dehydrogenase deficiency Investigating families with pyruvate kinase deficiency to determine inheritance pattern and for genetic counseling

**Interpretation:** Most hemolytic anemias due to pyruvate kinase (PK) deficiency are associated with activity levels less than 40% of mean normal. However, some patients with clinically significant hemolysis can have normal or only mildly decreased PK enzyme activity, which paradoxically may occur in individuals with the most severe symptoms. Carriers (heterozygotes) may show mildly decreased activity and are hematologically normal. Elevated PK concentrations can be found in those patients with younger erythrocyte population. This may be due to the patient being a newborn or young red cells are being produced in response to the anemia (reticulocytosis).

**Reference Values:**

> or =12 months: 6.7-14.3 U/g Hb

Reference values have not been established for patients who are <12 months of age.

**Pyruvate, Spinal Fluid**

**Clinical Information:** Pyruvate, an intermediate metabolite, plays an important role in linking carbohydrate and amino acid metabolism to the tricarboxylic acid cycle, the fatty acid beta-oxidation pathway, and the mitochondrial respiratory chain complex. Though pyruvate is not diagnostic in itself, analysis with lactate has diagnostic value as many inborn errors of metabolism present with laboratory findings that include lactic acidosis and/or a high lactate:pyruvate (L:P) ratio. The L:P ratio is elevated in several, but not all, mitochondrial respiratory chain disorders. Mitochondrial disorders vary widely in presentation and age of onset. Many mitochondrial disorders have neurologic and myopathic features and may involve multiple organ systems. Determination of lactate, pyruvate, and the L:P ratio in cerebrospinal fluid is helpful in directing attention toward a possible mitochondrial disorder in cases with predominantly neurologic dysfunction and normal blood lactate levels. A low L:P ratio is observed in inherited disorders of pyruvate metabolism including pyruvate dehydrogenase complex (PDHC) deficiency. Clinical presentation of PDHC deficiency can range from fatal congenital lactic acidosis to relatively mild ataxia or neuropathy. The most common features in infants and children with PDHC deficiency are delayed development and hypotonia. Seizures and ataxia are also frequent features. Other manifestations can include congenital brain malformations, degenerative changes including Leigh disease, and facial dysmorphism.

**Useful For:** Investigating possible disorders of mitochondrial metabolism, when used in conjunction with cerebrospinal fluid lactate collected at the same time to determine the lactate-to-pyruvate (L:P) ratio Evaluating patients with neurologic dysfunction and normal blood lactate-to-pyruvate L:P ratios

**Interpretation:** An elevated lactate-to-pyruvate (L:P) ratio may indicate inherited disorders of the respiratory chain complex, tricarboxylic acid cycle disorders and pyruvate carboxylase deficiency. Respiratory chain defects usually result in L:P ratios above 20. A low L:P ratio (disproportionately elevated pyruvic acid) may indicate an inherited disorder of pyruvate metabolism. Defects of the pyruvate dehydrogenase complex result in L:P ratios below 10. The L:P ratio is characteristically normal in other patients. An artifactually high ratio can be found in acutely ill patients.

**Reference Values:**

0.06-0.19 mmol/L

**Clinical References:**


**Pyruvic Acid, Blood**

**Clinical Information:** Pyruvic acid, an intermediate metabolite, plays an important role in linking carbohydrate and amino acid metabolism to the tricarboxylic acid cycle, the fatty acid beta-oxidation pathway, and the mitochondrial respiratory chain complex. Though isolated elevated pyruvate is not diagnostic of any inborn error of metabolism, analysis with lactate may suggest an inborn error of metabolism as some present with lactic acidosis and/or a high lactate-to-pyruvate (L:P) ratio. The L:P ratio is elevated in several, but not all, mitochondrial respiratory chain disorders. Mitochondrial disorders vary widely in presentation and age of onset. Many mitochondrial disorders have neurologic and myopathic features and may involve multiple organ systems. Determination of lactate, pyruvate, and the L:P ratio in cerebrospinal fluid is helpful in directing attention toward a possible mitochondrial disorder in cases with predominantly neurologic dysfunction and normal blood lactate levels, though further confirmatory testing will be required to establish a diagnosis. A low L:P ratio is observed in inherited
disorders of pyruvate metabolism including pyruvate dehydrogenase complex (PDHC) deficiency. Clinical presentation of PDHC deficiency can range from fatal congenital lactic acidosis to relatively mild ataxia or neuropathy. The most common features in infants and children with PDHC deficiency are delayed development and hypotonia. Seizures and ataxia are also frequent features. Other manifestations can include congenital brain malformations, degenerative changes including Leigh disease, and facial dysmorphism.

**Useful For:** Screening for possible disorders of mitochondrial metabolism, when used in conjunction with blood lactate collected at the same time to determine the lactate-to-pyruvate ratio

**Interpretation:** An elevated lactate-to-pyruvate (L:P) ratio may indicate inherited disorders of the respiratory chain complex, tricarboxylic acid cycle disorders and pyruvate carboxylase deficiency. Respiratory chain defects usually result in L:P ratios above 20. A low L:P ratio (disproportionately elevated pyruvic acid) may indicate an inherited disorder of pyruvate metabolism. Defects of the pyruvate dehydrogenase complex result in L:P ratios below 10. The L:P ratio is characteristically normal in other patients. An artificially high ratio can be found if the patient is acutely ill. Cerebrospinal fluid (CSF) L:P ratio may assist in evaluation of patients with neurologic dysfunction and normal blood L:P ratios. Blood and CSF specimens should be collected at the same time.

**Reference Values:**

- 0.08-0.16 mmol/L
- NIH Unit
- 0.7-1.4 mg/dL

**Clinical References:**

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**Q Fever Antibody, IgG and IgM, Serum**

**Clinical Information:** Q fever, a rickettsial infection caused by Coxiella burnetii, has been recognized as a widely distributed zoonosis with the potential for causing both sporadic and epidemic disease. The resistance of C burnetii to heat, chemical agents, and desiccation allows the agent to survive for extended periods outside the host. The infection is spread by the inhalation of infected material, mainly from sheep and goats. They shed the organism in feces, milk, nasal discharge, placental tissue, and amniotic fluid. The clinical spectrum of disease ranges from unapparent to fatal. Respiratory manifestations usually predominate; endocarditis and hepatitis can be complications. During the course of the infection, the outer membrane of the organism undergoes changes in its lipopolysaccharide structure, called phase variation. Differences in phase I and phase II antigen presentation can help determine if the infection is acute or chronic: -In acute Q fever, the phase II antibody is usually higher than the phase I titer, often by 4-fold, even in early specimens. Although a rise in phase I as well as phase II titers may occur in later specimens, the phase II titer remains higher. -In chronic Q fever, the reverse situation is generally seen. Serum specimens drawn late in the illness from chronic Q fever patients demonstrate significantly higher phase I titers, sometimes much greater than 4-fold. -In the case of chronic granulomatous hepatitis, IgG and IgM titers to phase I and phase II antigens are quite elevated, with phase II titers generally equal to or greater than phase I titers. -Titers seen in Q fever endocarditis are similar in magnitude, although the phase I titers are quite often higher than the phase II titers.

**Useful For:** Diagnosing Q fever

**Interpretation:** Phase I antibody titers greater than or equal to phase II antibody titers are consistent
with chronic infection or convalescent phase Q fever. Phase II antibody titers greater than or equal to phase I antibody titers are consistent with acute/active infection. A negative result argues against Coxiella burnetii infection. If early acute Q fever infection is suspected, draw a second specimen 2 to 3 weeks later and retest. In Q fever sera, it is common to see IgG titers of 1:128 or greater to both phase I and phase II antibody titers. IgG class antibody titers appear very early in the disease, reaching maximum phase II titers by week 8 and persisting at elevated titers for longer than a year. Phase I titers follow the same pattern, although at much lower levels, and may not be initially detected until convalescence. In Q fever sera, it is common to see IgM titers of 1:64 or greater. IgM class antibody titers appear very early in the disease, reaching maximum phase II titers by week 3 and declining to very low levels by week 14. Phase I titers follow the same pattern, although at much lower levels, and may not be initially detected until convalescence.

**Reference Values:**

<table>
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<tr>
<th>Test</th>
<th>Reference Value</th>
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<tr>
<td>Q FEVER PHASE II ANTIBODY, IgG</td>
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<tr>
<td>Q FEVER PHASE I ANTIBODY, IgM</td>
<td>&lt;1:16</td>
</tr>
<tr>
<td>Q FEVER PHASE II ANTIBODY, IgM</td>
<td>&lt;1:16</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Clinical References:**


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**Quad Screen (Second Trimester) Maternal, Serum**

**Clinical Information:** Multiple marker serum screening has become a standard tool used in obstetrical care to identify pregnancies that may have an increased risk for certain birth defects, including neural tube defects (NTD), trisomy 21 (Down syndrome), and trisomy 18 (Edwards syndrome). The screen is performed by measuring analytes in maternal serum that are produced by the fetus and the placenta. The analyte values along with maternal demographic information such as age, weight, gestational age, diabetic status, and race are used together in a mathematical model to derive a risk estimate. The laboratory establishes a specific cutoff for each condition, which classifies each screen as either screen-positive or screen-negative. A screen-positive result indicates that the value obtained exceeds the established cutoff. A positive screen does not provide a diagnosis, but indicates that further evaluation should be considered. Analytes: Alpha-Fetoprotein (AFP) AFP is a fetal protein that is initially produced in the fetal yolk sac and liver. A small amount also is transported from the amniotic fluid. The AFP concentration in maternal serum rises throughout pregnancy, from a nonpregnancy level of 0.2, to about 250 ng/mL at 32 weeks gestation. If the fetus has an open NTD, AFP is thought to leak directly into the amniotic fluid causing unexpectedly high concentrations of AFP. Subsequently, the AFP reaches the maternal circulation, thus producing elevated serum levels. Other fetal abnormalities such as omphalocele, gastroschisis, congenital renal disease, esophageal atresia, and other fetal distress situations such as threatened abortion, and fetal demise also may show AFP elevations. Increased maternal serum AFP values also may be seen in multiple pregnancies and in unaffected singleton pregnancies in which the gestational age has been underestimated. Lower maternal serum AFP values have been associated with an increased risk for genetic conditions such as trisomy 21 (Down syndrome) and trisomy 18. Estriol (uE3) Estriol, the principal circulatory estrogen hormone in the blood during pregnancy, is synthesized by the
intact feto-placental unit. Estriol exists in maternal blood as a mixture of the unconjugated form and a number of conjugates. The half-life of unconjugated estriol in the maternal blood system is 20 to 30 minutes because the maternal liver quickly conjugates estriol to make it more water soluble for urinary excretion. Estriol levels increase during the course of pregnancy. Decreased unconjugated estriol has been shown to be a marker for trisomy 21 and trisomy 18. Low levels of estriol also have been associated with overestimation of gestation, pregnancy loss, Smith-Lemli-Opitz, and X-linked ichthyosis (placental sulfatase deficiency). Human Chorionic Gonadotropin (Total Beta-hCG: ThCG) hCG is a glycoprotein consisting of 2 noncovalently bound subunits. The alpha subunit is identical to that of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH), while the beta subunit has significant homology to the beta subunit of LH and limited similarity to the FSH and TSH beta subunits. The beta subunit determines the unique physiological, biochemical, and immunological properties of hCG. The CGA gene (glycoprotein hormones, alpha polypeptide) is thought to have developed through gene duplication from the LH gene in a limited number of mammalian species. hCG only plays an important physiological role in primates (including humans), where it is synthesized by placental cells, starting very early in pregnancy, and serves to maintain the corpus luteum, and hence, progesterone production, during the first trimester. Thereafter, the concentration of hCG begins to fall as the placenta begins to produce steroid hormones and the role of the corpus luteum in maintaining pregnancy diminishes. Increased total hCG levels are associated with trisomy 21, while decreased levels may be seen in trisomy 18. Elevations of hCG also can be seen in multiple pregnancies, unaffected singleton pregnancies in which the gestational age has been overestimated, triploidy, fetal loss, and hydrops fetalis. Inhibin A Inhibins are a family of heterodimeric glycoproteins, primarily secreted by ovarian granulosa cells and testicular Sertoli cells, which consist of disulfide-linked alpha and beta subunits. While the alpha subunits are identical in all inhibins, the beta subunits exist in 2 major forms, termed A and B, each of which can occur in different isoforms. Depending on whether an inhibin heterodimer contains a beta A or a beta B chain, they are designated as inhibin A or inhibin B, respectively. Together with the related activins, which are homodimers or heterodimers of beta A and B chains, the inhibins are involved in gonadal-pituitary feedback and in paracrine regulation of germ cell growth and maturation. During pregnancy, inhibins and activins are produced by the feto-placental unit in increasing quantities, mirroring fetal growth. Their physiological role during pregnancy is uncertain. They are secreted into the coelomic and amniotic fluid, but only inhibin A is found in appreciable quantities in the maternal circulation during the first and second trimesters. Maternal inhibin A levels are correlated with maternal hCG levels and are abnormal in the same conditions that are associated with abnormal hCG levels (eg, inhibin A levels are typically higher in trisomy 21 pregnancies). However, despite their similar behavior, measuring maternal serum inhibin A concentrations in addition to maternal serum hCG concentrations further improves the sensitivity and specificity of maternal multiple marker screening for trisomy 21.

Useful For: Prenatal screening for open neural tube defect (alpha-fetoprotein only), trisomy 21 (alpha-fetoprotein, human chorionic gonadotropin, estriol, and inhibin A) and trisomy 18 (alpha-fetoprotein, human chorionic gonadotropin, and estriol)

Interpretation: Neural Tube Defects (NTD): A screen-negative result indicates that the calculated alpha-fetoprotein (AFP) multiple of the median (MoM) falls below the established cutoff of 2.50 MoM. A negative screen does not guarantee the absence of NTD. A screen-positive result indicates that the calculated AFP MoM is 2.50 MoM or greater, and may indicate an increased risk for open NTD. The actual risk depends on the level of AFP and the individual's pretest risk of having a child with NTD based on family history, geographical location, maternal conditions such as diabetes and epilepsy, and use of folate prior to conception. A screen-positive result does not infer a definitive diagnosis of NTD, but indicates that further evaluation should be considered. Approximately 80% of pregnancies affected with NTD have elevated AFP, MoM values greater than 2.5. Trisomy 21 (Down syndrome) and Trisomy 18 (Edwards syndrome): A screen-negative result indicates that the calculated screen risk is below the established cutoff of 1/270 for trisomy 21 and 1/100 for trisomy 18. A negative screen does not guarantee the absence of trisomy 21 or trisomy 18. When a trisomy 21 second-trimester risk cutoff of 1/270 is used for follow-up, the combination of maternal age, AFP, estriol, hCG, and inhibin A has an overall detection rate of approximately 77% to 81% with a false-positive rate of 6% to 7%. In practice, both the detection rate and false-positive rate increase with age. The detection rate ranges from 66% (early teens) to 99% (late 40s), with false-positive rates of between 3% and 62%, respectively. The detection rate for trisomy 18 is 60% to 80% using a second trimester cutoff of 1/100. Follow-up: Upon
receiving maternal serum screening results, all information used in the risk calculation should be reviewed for accuracy (maternal date of birth, gestational dating, etc.). If any information is incorrect, the laboratory should be contacted for a recalculation of the estimated risks. Screen-negative results typically do not warrant further evaluation. Ultrasound is recommended to confirm dates for NTD or trisomy 21 screen-positive results. Many pregnancies affected with trisomy 18 are small for gestational age. Recalculations that lower the gestational age may decrease the detection rate for trisomy 18. If ultrasound yields new dates that differ by at least 7 days, a recalculation should be considered. If dates are confirmed, high-resolution ultrasound and amniocentesis (including amniotic fluid AFP and acetylcholinesterase measurements for NTD) are typically offered.

Reference Values:

NEURAL TUBE DEFECTS
An AFP multiple of the median (MoM) <2.5 is reported as screen negative. AFP MoMs ≥ 2.5 (singleton and twin pregnancies) are reported as screen positive.

DOWN SYNDROME
Calculated screen risks <1/270 are reported as screen negative, risks ≥ 1/270 are reported as screen positive.

TRISOMY 18
Calculated screen risks <1/100 are reported as screen negative, risks ≥ 1/100 are reported as screen positive.

An interpretive report will be provided.


QuantiFERON-TB Gold Plus, Blood

Clinical Information: Latent tuberculosis infection (LTBI) is a noncommunicable, asymptomatic condition that persists for many years in individuals and may progress to active tuberculosis disease, particularly in immunosuppressed patients. The primary goal for diagnosis of LTBI is to initiate medical treatment in order to prevent progression to active disease. Historically, detection of LTBI has been done using the tuberculin skin test (TST). The TST has certain limitations however, including subjective interpretation, limited sensitivity in immunosuppressed patients, and the possibility of false-positive results in individuals who have received the bacille Calmette-Guerin (BCG) vaccine or are infected with other mycobacteria. The QuantiFERON-TB Gold Plus (QFT-Plus) test is an interferon (IFN)-gamma release assay (IGRA), which assesses the cell-mediated immune response to 2 Mycobacterium tuberculosis complex antigens, ESAT-6 and CFP-10, by measuring IFN-gamma levels in plasma. These 2 proteins are absent from all BCG strains and from most nontuberculosis mycobacteria with the exception of M kansasii, M szulgai and M marinum. Individuals infected with M tuberculosis complex agents, including M tuberculosis, M bovis, M africanum, M microti, M caprae, and M canetti, usually have lymphocytes in their blood that recognize these specific antigens and this recognition leads to the generation and secretion of IFN-gamma. This cytokine is subsequently detected and quantified using an IFN-gamma enzyme-linked immunosorbent assay. In an M tuberculosis infection, CD4+ T-cells play a critical role in immunological control through secretion of IFN-gamma. The prior version of the QFT-Plus assay, the QuantiFERON-TB Gold In-Tube (QFT-Gold) assay, only detected IFN-gamma.
secreted from CD4+ T-cells. Evidence now supports a role for CD8+ T-cells in host defense against M tuberculosis infection by likewise producing IFN-gamma, but by also stimulating macrophages to suppress the growth of M tuberculosis, to kill infected cells and to directly lyse intracellular M tuberculosis bacteria. IFN-gamma-producing M tuberculosis specific CD8+ T cells have been detected in subjects with LTBI and in patients with active TB. ESAT-6 and CFP-10 specific CD8+ T-cells have also been more frequently described in patients with active tuberculosis (TB) versus patients with LTBI, and have been detected in HIV-positive patients and children with TB disease. The QFT-Plus assay has 2 distinct TB antigen tubes: TB Antigen Tube 1 (TB1) and TB Antigen Tube 2 (TB2). Both tubes contain peptide antigens from ESAT-6 and CFP-10 for stimulation of a CD4+ T-cell IFN-gamma response. However, the TB2 tube also contains an additional set of ESAT-6 and CFP-10 peptides specifically designed to stimulate a CD8+ T-cell response. For the most up-to-date information regarding use of IGRAs, refer to the most recent guidelines on the Diagnosis of Tuberculosis in Adults and Children from the American Thoracic Society, the Infectious Diseases Society of America, the Centers for Disease Control and Prevention by DM Lewinsohn and colleagues.(1)

**Useful For:** Indirect test for Mycobacterium tuberculosis infection, to be used in conjunction with risk assessment, radiography, and other medical and diagnostic evaluations

**Interpretation:** A single positive result by this test should not be used solely to diagnose latent tuberculosis (TB). Results should be used in conjunction with risk assessment, radiography, and other medical and diagnostic evaluations. Positive: Interferon-gamma (IFN-gamma) response to Mycobacterium tuberculosis antigens detected, suggesting infection with M tuberculosis. Positive results in patients at low-risk for TB should be interpreted with caution and repeat testing on a new sample should be considered as recommended by the 2017 ATS/IDSA/CDC Clinical Practice Guidelines for Diagnosis of Tuberculosis in Adults and Children.(1) False-positive results may occur in patients with prior infection with M marinum, M szulgai, or M kanssii. Negative: No IFN-gamma response to M tuberculosis antigens was detected. Infection with M tuberculosis is unlikely. A single negative result does not exclude infection with M tuberculosis. In patients at high risk for M tuberculosis infection, a second test should be considered in accordance with the 2017 ATS/IDSA/CDC Clinical Practice Guidelines for Diagnosis of Tuberculosis in Adults and Children.(1) Indeterminate due to Low Mitogen Value: Indeterminate due to a low IFN-gamma level in the mitogen (positive control) tube. This may occur due to a low lymphocyte count, reduced lymphocyte activity, or inability of the patient's lymphocytes to generate IFN-gamma. Indeterminate due to High Nil value: Indeterminate due to a high level of IFN-gamma in the Nil (negative control) tube. This may occur due to heterophile antibody effects or nonspecific, circulating IFN-gamma in the patient's blood sample. Repeat testing on a new specimen is suggested.

**Reference Values:**
Negative


**Quantitative Lymphocyte Subsets: T, B, and Natural Killer (NK)**

**Clinical Information:** Lymphocytes in peripheral blood (circulation) are heterogeneous and can be broadly classified into T cells, B cells, and natural killer (NK) cells. There are various subsets of each of these individual populations with specific cell-surface markers and function. This assay provides absolute (cells/µL) and relative (%) quantitation for the main categories of T cells, B cells, and NK cells, in addition to a total lymphocyte count (CD45+). Each of these lymphocyte subpopulations have distinct effector and regulatory functions and are maintained in homeostasis under normal physiological conditions. Each of these lymphocyte subsets can be identified by a combination of one or more cell surface markers. The CD3 antigen is a pan-T cell marker, and T cells can be further divided into 2 broad
categories, based on the expression of CD4 or CD8 coreceptors. B cells can be identified by expression of CD19, while NK cells are typically identified by the coexpression of CD16 and CD56. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon with no change between noon and afternoon. NK-cell counts, on the other hand, are constant throughout the day.(1) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(2-4) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(2) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared to the evening(5) and during summer compared to winter.(6) These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets. Abnormalities in the number and percent of T (CD3, CD4, CD8), B (CD19), and NK (CD16+CD56) lymphocytes have been described in a number of different disease conditions. In patients who are infected with HIV, the CD4 count is measured for AIDS diagnosis and for initiation of antiviral therapy. The progressive loss of CD4 T-lymphocytes inpatients infected with HIV is associated with increased infections and complications. The Public Health Service has recommended that all HIV-positive patients be tested every 3 to 6 months for the level of CD4 T lymphocytes. Lymphocyte subset quantitation is also very useful in the evaluation of patients with primary immunodeficiencies of all ages, including follow-up for newborn screening for severe combined immunodeficiency (SCID) and immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, or any other relevant clinical condition where immunomodulatory treatment is used. It is also helpful as a preliminary screening assay for gross quantitative anomalies in any lymphocyte subset, whether related to malignancies or infection. The 2008 guidelines for diagnosis and treatment of Chronic Lymphocytic Leukemia (CLL) from the International Workshop on Chronic Lymphocytic Leukemia(7) recommends changing the diagnostic criteria for CLL from an absolute lymphocyte count (ALC) greater than 5 x 10^9/L to a circulating B-cell count greater than 5 x 10^9/L previously defined in the 1996 National Cancer Institute (NCI) guidelines for CLL. This flow cytometric assay enables accurate quantitation of circulating B cells using a single platform technology with absolute quantitation through the use of flow cytometry beads.

Useful For: Serial monitoring of CD4 T-cell count in HIV-positive patients Follow-up and diagnostic evaluation of primary immunodeficiencies, including severe combined immunodeficiency Immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, and other immunological conditions where such treatment is utilized Assessment of immune reconstitution post hematopoietic cell transplantation Early screening of gross quantitative anomalies in lymphocyte subsets in infection or malignancies Absolute quantitation of circulating B cells for diagnosis of chronic lymphocytic leukemia patients as indicated in the 2008 International Workshop on Chronic Lymphocytic Leukemia guidelines

Interpretation: When the CD4 count falls below 500 cells/mcL, HIV-positive patients can be diagnosed with AIDS and can receive antiretroviral therapy. When the CD4 count falls below 200 cells/mcL, prophylaxis against Pneumocystis jiroveci pneumonia is recommended.

Reference Values: The appropriate age-related reference values will be provided on the report.

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

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<th>Interpretation</th>
<th>kU/L</th>
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<tbody>
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<td>Negative</td>
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<tr>
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<td>Equivocal</td>
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<tr>
<td>2</td>
<td>Positive</td>
<td>0.70-3.49</td>
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<tr>
<td>3</td>
<td>Positive</td>
<td>3.50-17.4</td>
</tr>
<tr>
<td>4</td>
<td>Strongly positive</td>
<td>17.5-49.9</td>
</tr>
<tr>
<td>5</td>
<td>Strongly positive</td>
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</tr>
<tr>
<td>6</td>
<td>Strongly positive</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

Quetiapine (Seroquel)

Reference Values:

Units: ng/mL
Therapeutic and toxic ranges have not been established. Expected steady-state Quetiapine plasma levels in patients receiving recommended daily dosages: 100 - 1000 ng/mL.

Quinidine, Serum

Clinical Information: Quinidine is indicated for atrial fibrillation and flutter, and life-threatening ventricular arrhythmia. Optimal serum concentrations are in the range of 2.0 to 5.0 mcg/mL, with toxicity apparent at levels > or =6.0 mcg/mL. Symptoms of toxicity (cinchonism) include tinnitus, light-headedness, premature ventricular contractions, and atrioventricular block. Gastrointestinal distress is a frequent side effect, which becomes more severe and is associated with nausea and vomiting at higher drug concentrations. The half-life of quinidine is 6 to 8 hours, and the drug lacks any significant active metabolites. Physiologic processes that generally reduce hepatic metabolism and renal clearance increase serum quinidine levels, while comedication with cytochrome p450 (CYP) enzyme inducers enhances clearance and results in lower blood concentrations.

Useful For: Assessing and adjusting dosage for optimal therapeutic level Assessing toxicity

Interpretation: Optimal response to quinidine occurs when the serum level is between 2.0 to 5.0 mcg/mL.

Reference Values:
Therapeutic: 2.0-5.0 mcg/mL
Critical value: > or =6.0 mcg/mL


Quinoa (Chenopodium quinoa) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal/Borderline 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 High Positive 4 17.50 â€“ 49.99 Very High Positive 5 50.00 â€“ 99.99 Very High Positive 6 >99.99 Very High Positive

Reference Values:
<0.35 kU/L

Rabbit Epithelium, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease
and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Referece values apply to all ages.


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**Rabbit Meat, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com

RSER 82544

Rabbit Serum Proteins, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms Identifying allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Rabbit Urine Proteins, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms Identifying allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


Rabies Antibody Endpoint

Interpretation: Quantitative results. For those who want to know their exact titer between the reportable range. RFFIT stands for Rapid Fluorescent Foci Inhibition Test. It is a serum neutralization (inhibition) test, which means it measures the ability of rabies specific antibodies to neutralize rabies virus and prevent the virus from infecting cells. The antibodies are called rabies virus neutralizing antibodies (RVNA).

Reference Values:

Reportable range is 0.1 to 15.0 IU/mL
Less than 0.1 IU/mL: Below detection limit

In humans a results of 0.5 IU/mL or higher is considered an acceptable response to rabies vaccination according to the World Health Organization (WHO) guidelines; see WHO and Advisory Committee on Immunization Practices documents for additional guidance.

**Radish (Raphanus sativus) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

**Raji Cell Immune Complex Assay**

**Reference Values:**
<= 37 ugE/mL

Many autoimmune disorders, chronic infections and malignancies are associated with circulating immune complexes. Quantitation of immune complexes assists in staging immunologic disorders.

**Rape Seed, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms Identifying allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

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**Rapid Malaria/Babesia Smear**

**Clinical Information:** Malaria is a major tropical disease infecting approximately 500 million people and causing 1.5 to 2.7 million deaths annually. Ninety percent of the deaths occur in sub-Saharan Africa and most of these occur in children less than 5 years old; it is the leading cause of mortality in this age group. This disease is also widespread in Central and South America, Hispaniola, the Indian subcontinent, the Middle East, Oceania, and Southeast Asia. In the United States, individuals at risk include travelers to, and visitors from endemic areas. Malaria is caused primarily by 4 species of the protozoan Plasmodium: P falciparum, P vivax, P malariae, and P ovale. A fifth Plasmodium species, P knowlesi, is a similar parasite that may be an important source of human infection in some regions of Southeast Asia. Differentiating P falciparum and P knowlesi from other species is important since both can cause life-threatening infections. In addition, P falciparum is typically resistant to many commonly used antimalarial agents such as chloroquine. Babesiosis is an emergent zoonosis caused by an intraerythrocytic protozoan in the genus Babesia. B microti is responsible for the vast majority of human cases in the United States, with "hot spots" of disease along the Northeast Coast (e.g., Martha's Vineyard, Long Island, and Nantucket) and Midwest states, although the distribution of disease is spreading. In addition, a small number of cases of B duncani and B duncani-like human infection (WA and CA strains) have been reported along Pacific Coast states from Washington to northern California, and B divergens/B divergens-like strains have been isolated from humans in Missouri (MO-1 strain), Kentucky, and Washington. At this time, only B microti is a nationally notifiable disease. B microti shares a tick vector with Borrelia burgdorferi and Anaplasma phagocytophilum, the causative agents of Lyme disease and human granulocytic anaplasmosis (HGA), respectively. Recent studies suggest that exposure to B microti is quite common in areas endemic for Lyme disease and anaplasmosis, so it is prudent to consider testing for all 3 diseases concurrently. Less commonly, babesiosis may be acquired through blood transfusion, and therefore the FDA approved testing for this parasite in donor units in 2018. Most patients with babesiosis have a mild illness or are asymptomatic, but some develop a severe illness that may result in death. Patient symptoms may include fever, chills, extreme fatigue, and severe anemia. The most severe cases occur in asplenic individuals and those over 50 years of age. Rare cases of chronic parasitemia, usually in immunocompromised patients, have been described. Microscopy of Giemsa-stained thick and thin blood films is the standard laboratory method for diagnosis and differentiation of Plasmodium and Babesia species. Under optimal conditions, the sensitivity of the thick film microscopy is estimated to be 10 to 30 parasites per microliter of blood. This test can also detect trypanosomes that cause Chagas disease (Trypanosoma cruzi) and African sleeping sickness (Trypanosoma brucei), as well as some species of filariae. If filarial infection is suspected, FIL / Filaria, Blood is recommended since it is more sensitive than the traditional blood smear examination. Examination of the thin film allows for calculation of malaria percent parasitemia, which can be used to predict prognosis and monitor response to treatment for patients with malaria and babesiosis. The percentage parasitemia represents the percentage of infected red blood cells. This is calculated from representative microscopic fields on the thin blood film. Malarial gametocytes are not included in the calculation since they are not infectious to humans and are not killed by most antimalaria drugs.

**Useful For:** Rapid and accurate detection and species identification of Plasmodium Detection of Babesia, trypanosomes, and some species of microfilariae

**Interpretation:** A positive smear indicates infection with the identified species of Plasmodium or with Babesia. Species identification can indicate the appropriate antimalarial therapy.

**Reference Values:**

Negative

If positive, organism identified and percent parasitemia calculated, if applicable.

**Clinical References:** Hoffman SL: Diagnosis, treatment, and prevention of malaria. Med Clin North Am 1992;76:1327-1355

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**Rapid Plasma Reagin (RPR), Response to Therapy, Serum**

**Clinical Information:** Syphilis is a disease caused by infection with the spirochete Treponema
pallidum. The infection is systemic and the disease is characterized by periods of latency. These features, together with the fact that T pallidum cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis. Patients with primary or secondary syphilis should be reexamined clinically and serologically 6 months and 12 months following treatment. Typically, rapid plasma reagin titers decrease following successful treatment, but this may occur over a period of months to years.

**Useful For:** Determining the current disease status and evaluating response to therapy for syphilis

**Interpretation:** Treatment response is generally indicated by a 4-fold (2-tube dilution) reduction in rapid plasma reagin (RPR) titer (eg, from 1:32 to 1:8). For proper interpretation of RPR results, titers should be obtained using the same testing method and, preferably, at the same testing laboratory. Failure of nontreponemal test titers to decline 4-fold within 6 months after therapy for primary or secondary syphilis may be indicative of treatment failure. Patients whose titers remain serofast should be reevaluated for HIV infection.

**Reference Values:**
Negative

**Clinical References:**

**RAS/RAF Targeted Gene Panel by Next-Generation Sequencing, Tumor**

**Clinical Information:** Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the US Food and Drug Administration (FDA) for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Next generation sequencing has recently emerged as an accurate, cost-effective method to identify mutations across numerous genes known to be associated with response or resistance to specific targeted therapies. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with solid tumors. These data can also be used to help determine clinical trial eligibility for patients with mutations in genes not amenable to current FDA-approved targeted therapies. The epidermal growth factor receptor (EGFR) gene product is activated by the binding of specific ligands (epiregulin and amphiregulin), resulting in activation of the RAS/MAPK pathway. Activation of this pathway induces a signaling cascade ultimately regulating a number of cellular processes including cell proliferation. Dysregulation of the RAS/MAPK pathway is a key factor in tumor progression. Targeted therapies directed to EGFR, which inhibit activation of the RAS/MAPK pathway, have demonstrated some success (increased progression-free and overall survival) in patients with colorectal cancer. Assessment for BRAF mutations has clinical utility in that it is a predictor of response to antimitant BRAF therapy. BRAF is a member of the mitogen-activated protein/extracellular signal-regulated (MAP/ERK) kinase pathway, which plays a role in cell proliferation and differentiation. Dysregulation of this pathway is a key factor in tumor progression. Targeted therapies directed to components of this pathway have demonstrated some success with increases both in progression-free and overall survival in patients with certain tumors. Effectiveness of these therapies, however, depends in part on the mutation status of the pathway components. See Targeted Gene Regions Interrogated by RAS/RAF Gene Panel in Special Instructions for details regarding the targeted gene regions identified by this test.

**Useful For:** Identifying tumors that may respond to targeted therapies by assessing multiple gene targets simultaneously Identifying mutations that may help determine prognosis for patients with solid tumors Identifying specific mutations within genes known to be associated with response or resistance to specific cancer therapies

**Interpretation:** An interpretive report will be provided.
Reference Values:
An interpretive report will be provided.


FRASP
57665

Raspberry IgG
Interpretation: mcg/mL of IgG
Lower Limit of Quantitation: 2.0
Upper Limit of Quantitation: 200

Reference Values:
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

RASP
86305

Raspberry, IgE
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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**Rat Epithelium, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Rat Serum Protein, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Rat Urine Protein, IgE

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**FRMTA 75310**

Recombx MaTa Autoantibody Test

**Reference Values:**

A final report will be attached in MayoAccess.

**EEEVP 84161**

Red Blood Cell (RBC) Enzyme Evaluation

**Clinical Information:** All enzyme defects, including erythrocyte enzyme errors, are inherited; some are sex-linked and located on the X chromosome. Some family members have no hematologic abnormalities, while others have a hemolytic anemia. For a number of RBC enzyme defects (eg, deficiencies of hexokinase, glucose phosphate isomerase, pyruvate kinase), the sole clinical manifestation is hemolytic anemia. Glucose-6-phosphate dehydrogenase deficiency is the most common metabolic error of the red cell and presents with acute hemolytic anemia in response to oxidant stress (eg, drugs, acute infections, fava bean ingestion). This is a consultative evaluation looking at red cell enzyme defects as the cause for early red cell destruction.
Useful For: Identifying defects of red cell enzyme metabolism Evaluating patients with hemolytic anemia

Interpretation: A hematopathologist expert in these disorders evaluates the case, appropriate tests are performed, and an interpretive report is issued.

Reference Values: Definitive results and an interpretive report will be provided.


Red Blood Cell Enzyme Sequencing, Varies

Clinical Information: Next-generation sequencing (NGS) is a methodology that can interrogate large regions of genomic DNA in a single assay. The presence and pattern of gene mutations can provide critical diagnostic, prognostic, and therapeutic information for managing physicians. This panel aids in the diagnosis and genetic counseling of individuals with inherited RBC enzymopathies, possible carrier states, or compound mutations with severity modulating interactions. This panel always should be interpreted in the context of protein functional findings by enzymatic assay and complete blood count and peripheral blood findings. This complete interpretation can be provided by also ordering the EEEVP / RBC Enzyme Evaluation. Please fill out the information sheet and indicate that NGS testing was ordered. Providing CBC data and clinical notes will also allow more precise interpretation of results. Mature erythrocytes are dependent upon glycolysis for energy production and the hexose monophosphate shunt for oxidation-reduction stability. Hereditary deficiencies in RBC enzymes within these pathways cause nonspherocytic hemolytic anemia (NSHA) with variable clinical presentations, therapeutic considerations and inheritance patterns.(1-3) Most of these deficiencies cause chronic hemolysis with little to no pathognomonic morphologic changes in the peripheral blood smear making correlation with enzyme activity critical for diagnosis. Some are associated with acute episodic anemia triggered by medications, food, or viral illness. Variable additional symptoms may be present for some deficiency types, including myopathy, neuropathy, and developmental delay. Because a subset of clinically significant RBC enzyme disorders can have indeterminate to normal enzyme activity (masking in the presence of increased reticulocytes), the protein (enzymatic activity) studies are more sensitive when performed as a panel of RBC enzymes, which allows comparison of multiple enzyme activities. This genetic panel can aid in the interpretation of equivocal protein findings and genetically confirm an enzyme deficiency. Additionally, there are genes interrogated on this panel for which an enzyme test is not clinically available for correlation.

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of an underlying RBC enzymopathy Identifying mutations within genes associated with phenotypic severity, allowing for predictive testing and further genetic counseling

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(4,5) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values: An interpretive report will be provided.

Red Blood Cell Membrane Evaluation, Blood

Clinical Information: The functional red cell membrane is composed of a cholesterol and phospholipid bilayer anchored by integral proteins to an elastic cytoskeletal network. These interactions form the shape, deformability, and proper ion balance of the cell. Abnormalities in these moieties result in red blood cell membrane disorders. Hereditary spherocytosis (HS) is a common membrane disorder that can be present in many ethnic groups. Its prevalence has been estimated at approximately 1 in 3,000 persons of Northern European ancestry. It is usually associated with visible spherocytes on the peripheral blood smear and can be associated with variable clinical features of hemolysis ranging from completely compensated to mild to severe. Hereditary elliptocytosis (HE) is another fairly common and clinically variable disorder that can range from normal RBC indices in the large majority of cases to rare patients with moderate to severe anemia. Common hereditary elliptocytosis (CHE) is characterized by the presence of elliptocytes on the peripheral blood smear. Mutations associated with HE have been reported in widely variable ethnicities with greater prevalence in populations overlapping the malaria belt. Hereditary pyropoikilocytosis (HPP) is best classified as a severe form of hereditary elliptocytosis. It is uncommon and presents in early childhood as a severe hemolytic anemia. These disorders are associated with marked poikilocytosis on the peripheral blood smear.(1,2) Red cell membrane disorders can result from abnormalities involving several red cell membrane proteins, such as band 3, alpha and beta spectrin, protein 4.1, protein 4.2, glycoporphin C, and ankyrin. Most often, red cell membrane disorders are diagnosed in childhood, adolescence, or early adult life. The diagnosis of HS is usually made by a combination of patient and family history, laboratory evidence of hemolysis, and review of a peripheral blood smear. The osmotic fragility (OF) test is usually markedly abnormal in HS cases. However, factors such as age, iron status, and medications can affect the OF test. The OF test is nonspecific and can be increased in acquired disorders such as autoimmune hemolytic anemia. Coombs testing should be negative prior to ordering this test. The addition of eosin-5-maleimide (EMA) binding (Band3) flow cytometry to this profile increases specificity if a typical moderately decreased pattern is present. Hereditary pyropoikilocytosis can have normal or only mildly increased OF results and often displays a very dim and sometimes dual peak pattern with EMA-binding testing. Common hereditary elliptocytosis cases are not discriminated from normal patients in either OF and EMA binding (band3) testing and this profile does not add confirmatory information for HE.

Useful For: Investigation of suspected red cell membrane disorders such as hereditary spherocytosis or hereditary pyropoikilocytosis

Interpretation: An interpretive report will be provided.

Reference Values:
> or =12 months:
0.50 g/dL NaCl (unincubated): 3-53% hemolysis
0.60 g/dL NaCl (incubated): 14-74% hemolysis
0.65 g/dL NaCl (incubated): 4-40% hemolysis
0.75 g/dL NaCl (incubated): 1-11% hemolysis
An interpretive report will be provided.

Reference values have not been established for patients who are <12 months of age.

Red Blood Cell Membrane Sequencing, Varies

Clinical Information: Next-generation sequencing (NGS) is a methodology that can interrogate large regions of genomic DNA in a single assay. The presence and pattern of gene mutations can provide critical diagnostic, prognostic, and therapeutic information for managing physicians. This test is best interpreted in the context of protein studies and peripheral blood findings. This can be provided by also ordering the RBCME / Red Blood Cell Membrane Evaluation test. Please fill out the information sheet and indicate that NGS testing was ordered. Providing CBC data and clinical notes will also allow more precise interpretation of results. This panel aids in the diagnosis and genetic counseling of individuals with RBC membrane disorders including hereditary spherocytosis, hereditary elliptocytosis, hereditary pyropoikilocytosis, Southeast Asian ovalocytosis, hereditary stomatocytosis (both overhydrated and dehydrated/hereditary xerocytosis subtypes), and cryohydrocytosis (1-3). The functional red cell membrane is composed of a cholesterol and phospholipid bilayer anchored by integral proteins to an elastic cytoskeletal network. These interactions form the shape, deformability, and proper ion balance of the cell. Abnormalities in these moieties result in red blood cell membrane disorders. Hereditary spherocytosis (HS) is a common membrane disorder that can be present in all ethnic groups. It is usually associated with visible spherocytes on the peripheral blood smear and can be associated with variable clinical features of hemolysis ranging from mild to severe. Paradoxically, erythrocytosis can occur after splenectomy. Hereditary elliptocytosis (HE) is another fairly common and clinically variable disorder that can range from normal RBC indices in the large majority of cases to a minor subset of patients with moderate to severe anemia. Common hereditary elliptocytosis (CHE) is characterized by the presence of elliptocytes on the peripheral blood smear and the absence of anemia. Mutations associated with HE have been reported in widely variable ethnicities with greater prevalence in populations overlapping the malaria belt. Hereditary pyropoikilocytosis (HPP) is now best classified as a severe form of hereditary elliptocytosis. It is uncommon and presents in early childhood as a severe hemolytic anemia. These disorders are associated with marked poikilocytosis on the peripheral blood smear. (1,2) Hereditary stomatocytosis is an RBC membrane permeability disorder that can manifest as the more common dehydrated hereditary stomatocytosis (DHSi), also known as hereditary xerocytosis (HX), and the rarer overhydrated hereditary stomatocytosis (OHSt) subtypes. These disorders are important to confirm or exclude as splenectomy has been associated with an increased risk for serious venous thrombosis and thromboembolism events and is contraindicated in published guidelines. (4) DHSi/HX manifests variably as mild to compensated anemia to some cases with increased hemoglobin levels. Some patients are asymptomatic, others show hemolysis after even nontraumatic exercise sessions. Others display perinatal edema and susceptibility to iron overload. DHSi/HX is associated with pseudohyperkalemia, increased MCHC, and decreased osmotic fragility due to relative dehydration of the red blood cell. OHSt is similarly associated with anemia of variably severity, but is associated with increased osmotic fragility due to a relatively overhydrated steady state.

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of an RBC membrane disorder Second-tier testing for patients in whom previous targeted gene mutation analyses were negative for a specific RBC membrane disorder Establishing a diagnosis of a hereditary RBC membrane disorder, allowing for appropriate management and surveillance of disease features based on the gene involved, especially if splenectomy is a consideration (4) Identifying mutations within genes associated with phenotypic severity, allowing for predictive testing and further genetic counseling

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. (5,6) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical
Red Currant, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Red Snapper (Lutjanus spp) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal/Borderline 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 High Positive 4 17.50-49.99 Very High Positive 5 50.00-99.99 Very High Positive 6 >99.99 Very High Positive

**Reference Values:**
<0.35 kU/L

Red Sorrel, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
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Red Top, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>5</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Reducing Substance, Feces

Clinical Information: Testing for fecal reducing substances (carbohydrates) aids in determining the underlying cause of diarrhea. Elevations in fecal reducing substances helps distinguish between osmotic diarrhea caused by abnormal excretion of various sugars as opposed to diarrhea caused by viruses and parasites. Increased reducing substances in stool are consistent with, but not diagnostic of, primary or secondary disaccharidase deficiency (primarily lactase deficiency) or intestinal monosaccharide malabsorption. Similar intestinal absorption deficiencies are associated with short bowel syndrome and necrotizing enterocolitis.

Useful For: Assisting in the differentiation between osmotic and nonosmotic diarrhea Screening test for: -Diarrhea from disaccharidase deficiencies, (eg, lactase deficiency) -Monosaccharide malabsorption

Interpretation: Negative: negative Normal: < or =0.25 g/dL (trace) Suspicious: >0.25 to 0.50 g/dL
(grade 1) Abnormal: >0.50 g/dL (grade 2-4)

Reference Values:
Negative or trace

Clinical References:

Relative B-Cell Subset Analysis Percentage

Clinical Information: The adaptive immune response includes both cell-mediated (mediated by T cells and NK cells) and humoral immunity (mediated by B cells). After antigen recognition and maturation in secondary lymphoid organs, some antigen-specific B cells terminally differentiate into antibody-secreting plasma cells or become memory B cells. Memory B cells are of 3 subsets: marginal zone B cells (MZ or nonswitched memory), class-switched memory B cells, and IgM-only memory B cells. Decreased B-cell numbers, B-cell function, or both, result in immune deficiency states and increased susceptibility to infections. These decreases may be either primary (genetic) or secondary. Secondary causes include medications, malignancies, infections, and autoimmune disorders. Common variable immunodeficiency (CVID), a disorder of B-cell function, is the most prevalent primary immunodeficiency with a prevalence of 1:25,000 to 1:50,000.(1) CVID has a bimodal presentation with a subset of patients presenting in early childhood and a second set presenting between 15 and 40 years of age, or occasionally even later. Four different genetic defects have been associated with CVID, including mutations in the ICOS, CD19, BAFF-R, and TACI genes. The first 3 genetic defects account for approximately 1% to 2%, and TACI mutations account for 8% to 15% of CVID cases. CVID is characterized by hypogammaglobulinemia usually involving most or all of the Ig classes (IgG, IgA, IgM, and IgE), impaired functional antibody responses, and recurrent sinopulmonary infections.(1,2) B-cell numbers may be normal or decreased. A minority of CVID patients (5%-10%) have very low B-cell counts (<1% of peripheral blood leukocytes), while another subset (5%-10%) exhibit noncaseating, sarcoid-like granulomas in different organs and also tend to develop a progressive T-cell deficiency.(1) Of all patients with CVID, 25% to 30% have increased numbers of CD8 T cells and a reduced CD4:CD8 ratio (<1). Studies have shown the clinical relevance of classifying CVID patients by assessing B-cell subsets, since changes in different B-cell subsets are associated with particular clinical phenotypes or presentations.(3,4) The B-cell phenotyping assay can be used in the diagnosis of hyper-IgM syndromes, which are characterized by increased or normal levels of IgM with low IgG and/or IgA.(5) Patients with hyper-IgM syndromes can have 1 of 5 known genetic defectsâ€”mutations in the CD40, CD40, AID (activation-induced cytidine deaminase), UNG (uracil DNA glycosylase), and NEMO (NF-kappa B essential modulator) genes.(5) Mutations in CD40 and NEMO are inherited in an X-linked fashion, while mutations in the other 3 genes are inherited in an autosomal recessive fashion. Patients with hyper-IgM syndromes have a defect in isotype class-switching, which leads to a decrease in class-switched memory B cells, with or without an increase in nonswitched memory B cells and IgM-only memory B cells. In addition to its utility in the diagnosis of the above-described primary immunodeficiencies, B-cell phenotyping may be used to assess reconstitution of B-cell subsets after hematopoietic stem cell or bone marrow transplant. This test is also used to monitor B-cell-depleting therapies, such as Rituxan (Rituximab) and Zevalin (Ibritumomab tiuxetan).

Useful For:
Screening for humoral or combined immunodeficiencies, including common variable immunodeficiency (CVID), hyper IgM syndrome, among others, where B-cell subset distribution information is desired Assessing B-cell subset reconstitution after hematopoietic cell (HCT) or bone marrow transplant Assessing B-cell subset reconstitution following recovery of B cells after
B-cell-depleting immunotherapy

**Interpretation:** The assay provides semiquantitative (%) information on the various B-cell subsets. Each specimen is evaluated for B-cell subsets with respect to the total number of CD19+ B cells present in the peripheral blood mononuclear cell population, compared to the reference range. In order to verify that there are no CD19-related defects, CD20 is used as an additional pan-B-cell marker (expressed as percentage of CD45+ lymphocytes). The B-cell panel assesses the following B-cell subsets: -CD19+=B cells expressing CD19 as a percent of total lymphocytes -CD19+ CD27+ IgD+ IgM+=marginal zone or non-switched memory B cells -CD19+ CD27+ IgD- IgM+=IgM-only memory B cells -CD19+ CD27+ IgD- IgM-=class-switched memory B cells -CD19+ IgM+=IgM B cells -CD19+ CD38+ IgM+=transitional B cells -CD19+ CD38+ IgM-=plasmablasts -CD19+ CD21-=CD21-negative B cells -CD19+ CD21+ IgD- CD27-=CD21-positive B cells -CD19+ CD20+=B cells co-expressing both CD19 and CD20 as a percent of total lymphocytes For isotype class-switching and memory B-cell analyses, the data will be reported as being consistent or not consistent with a quantitative defect in memory subsets and/or class switching. If a defect is present in any of these B-cell subpopulations, further correlation with clinical presentation and additional functional, immunological, and genetic laboratory studies will be suggested, if appropriate.

**Reference Values:**
The appropriate age-related reference values will be provided on the report.

**Clinical References:**

**TFEBF 64973**

**Renal Cell Carcinoma, 6p21.1 (TFEB) Rearrangement, FISH, Tissue**

**Clinical Information:** The TFEB gene may be altered in some patients with renal cell carcinoma (RCC). Identification of rearrangement of the TFEB gene region by FISH analysis can aid in the diagnosis of RCC.

**Useful For:** Identifying TFEB gene rearrangements in patients with renal cell carcinoma (RCC)

**Interpretation:** A positive result with the TFEB probe is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result of TFEB suggests promoter substitution caused by structural alterations of the TFEB gene region at 6p21.1. A negative result suggests no structural alterations of the locus.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
Renal Function Panel, Serum

**Clinical Information:** A renal function panel could be ordered when a patient has risk factors for kidney dysfunction such as high blood pressure (hypertension), diabetes, cardiovascular disease, obesity, elevated cholesterol, or a family history of kidney disease. A renal function panel may also be ordered when someone has signs and symptoms of kidney disease, though early kidney disease often does not cause any noticeable symptoms. It may be initially detected through routine blood or urine testing.

**Useful For:** Aids in diagnosis and management of conditions affecting kidney function General health screening Screening patients at risk of developing kidney disease Management of patients with known kidney disease

**Interpretation:** Renal function panel results are not diagnostic but rather indicate that there may be a problem with the kidneys and that further testing is required to make a diagnosis and determine the cause. Results of the panel are usually considered together, rather than separately. Individual test result can be abnormal due to causes other than kidney disease, but taken together with risks and signs and symptoms, they may give an indication of whether kidney disease is present.

**Reference Values:**

<table>
<thead>
<tr>
<th>Test</th>
<th>&lt;1 year: not established</th>
<th>≥1 year: 135-145 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>SODIUM</td>
<td></td>
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<tr>
<td>POTASSIUM</td>
<td>&lt;1 year: not established</td>
<td>&gt; or =1 year: 3.6-5.2 mmol/L</td>
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<tr>
<td>CHLORIDE</td>
<td>&lt;1 year: not established</td>
<td>1-17 years: 102-112 mmol/L</td>
</tr>
<tr>
<td></td>
<td>≥18 years: 98-107 mmol/L</td>
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<tr>
<td>BICARBONATE</td>
<td>Males</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;1 year: not established</td>
<td>1-2 years: 17-25 mmol/L</td>
</tr>
<tr>
<td></td>
<td>1-2 years: 17-25 mmol/L</td>
<td>3 years: 18-26 mmol/L</td>
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<tr>
<td></td>
<td>4-5 years: 19-27 mmol/L</td>
<td>6-7 years: 20-28 mmol/L</td>
</tr>
<tr>
<td></td>
<td>8-17 years: 21-29 mmol/L</td>
<td>&gt; or =18 years: 22-29 mmol/L</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td></td>
</tr>
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<td></td>
<td>&lt;1 year: not established</td>
<td>1-3 years: 18-25 mmol/L</td>
</tr>
<tr>
<td></td>
<td>1-3 years: 18-25 mmol/L</td>
<td>4-5 years: 19-26 mmol/L</td>
</tr>
<tr>
<td></td>
<td>6-7 years: 20-27 mmol/L</td>
<td>8-9 years: 21-28 mmol/L</td>
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<td></td>
<td>&gt; or =10 years: 22-29 mmol/L</td>
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<tr>
<td>ANION GAP</td>
<td>&lt;7 years: not established</td>
<td>&gt; or =7 years: 7-15</td>
</tr>
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<td>BLOOD UREA NITROGEN (BUN)</td>
<td></td>
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<tr>
<td>Males</td>
<td>&lt;12 months: not established</td>
<td>1-17 years: 7-20 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&gt; or =18 years: 8-24 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
<12 months: not established
1-17 years: 7-20 mg/dL
> or =18 years: 6-21 mg/dL

**CREATININE**

**Males**
- 0-11 months: 0.17-0.42 mg/dL
- 1-5 years: 0.19-0.49 mg/dL
- 6-10 years: 0.26-0.61 mg/dL
- 11-14 years: 0.35-0.86 mg/dL
- > or =15 years: 0.74-1.35 mg/dL

**Females**
- 0-11 months: 0.17-0.42 mg/dL
- 1-5 years: 0.19-0.49 mg/dL
- 6-10 years: 0.26-0.61 mg/dL
- 11-15 years: 0.35-0.86 mg/dL
- > or =16 years: 0.59-1.04 mg/dL

**eGFR**

>60 mL/min/BSA

Estimated GFR calculated using the 2009 CKD_EPI creatinine equation.

**CALCIUM**

- <1 year: 8.7-11.0 mg/dL
- 1-17 years: 9.3-10.6 mg/dL
- 18-59 years: 8.6-10.0 mg/dL
- 60-90 years: 8.8-10.2 mg/dL
- >90 years: 8.2-9.6 mg/dL

**GLUCOSE**

- 0-11 months: not established
- > or =1 year: 70-140 mg/dL

**Total Protein**

- > or =1 year: 6.3-7.9 g/dL

Reference values have not been established for patients who are <12 months of age.

**ALBUMIN**

- > or =12 months: 3.5-5.0 g/dL

Reference values have not been established for patients who are <12 months of age.

**PHOSPHORUS**

**Males**
- 1-4 years: 4.3-5.4 mg/dL
- 5-13 years: 3.7-5.4 mg/dL
- 14-15 years: 3.5-5.3 mg/dL
- 16-17 years: 3.1-4.7 mg/dL
- > or =18 years: 2.5-4.5 mg/dL

Reference values have not been established for patients that are less than 12 months of age.

**Females**
- 1-7 years: 4.3-5.4 mg/dL
- 8-13 years: 4.0-5.2 mg/dL
- 14-15 years: 3.5-4.9 mg/dL
- 16-17 years: 3.1-4.7 mg/dL
- > or =18 years: 2.5-4.5 mg/dL

Reference values have not been established for patients that are less than 12 months of age.

**Clinical References:** 1. Oh MS: Evaluation of renal function, water, electrolytes, and acid-base balance. In Henry's Clinical Diagnosis and Management by Laboratory Methods. 22nd edition. Edited
Renal Pathology Consultation, Wet Tissue

Clinical Information: The Mayo Renal Pathology service is staffed by board-certified pathologists who have a special interest in non-neoplastic diseases of the kidney. Kidney biopsy has proven to be of value in the clinical evaluation and management of patients with kidney disease, including acute and chronic renal insufficiency, nephrotic syndrome, nephritic syndrome, proteinuria and hematuria, and in the overall management of renal transplant recipients. Optimal interpretation of a kidney biopsy requires integration of clinical and laboratory results with light microscopic, immunofluorescent histology, and electron microscopy findings.

Useful For: Evaluating and managing patients with kidney disease Following the progression of known renal disease or response to therapy Determining the cause of dysfunction in the transplanted kidney (allograft)

Interpretation: Both a verbal report and a faxed report are provided to nephrologists for Mayo Medical Laboratories cases. Representative electron microscopy images and significant positive immunofluorescent stain findings can be provided on a CD upon request. In most cases, the electron microscopy results are reported as an addendum and a final report is issued including these findings. This final report is again faxed to the submitting nephrologist and mailed to the submitting pathology laboratory, along with a representative set of the light microscopy slides.

Reference Values: An interpretive report will be provided.


Renin Activity, Plasma

Clinical Information: The renal juxtaglomerular apparatus generates renin, an enzyme that converts angiotensinogen to angiotensin I. The inactive angiotensin I is enzymatically converted to the active octapeptide angiotensin II, a potent vasopressor responsible for hypertension of renal origin. Angiotensin II also stimulates the zona glomerulosa of the adrenal cortex to release aldosterone. Renin secretion by the kidney is stimulated by a fall in glomerular blood pressure, by decreased sodium concentration at the macula densa at the distal tubule, or by stimulation of sympathetic outflow to the kidney, such as in renal vascular diseases.

Useful For: Investigation of primary aldosteronism (eg, adrenal adenoma/carcinoma and adrenal cortical hyperplasia) and secondary aldosteronism (renovascular disease, salt depletion, potassium loading, cardiac failure with ascites, pregnancy, Bartter syndrome) Not useful for determination of plasma renin concentration.

Interpretation: A high ratio of serum aldosterone (SA) in ng/dL to plasma renin activity (PRA) in ng/mL per hour, is a positive screening test result, a finding that warrants further testing. A SA:PRA ratio > or =20 and SA of > or =15 ng/dL indicates probable primary aldosteronism. Renal disease, such as unilateral renal artery stenosis, results in elevated renin and aldosterone levels. Renal venous catheterization may be helpful. A positive test is a renal venous renin ratio (affected:normal) above 1.5. See Renin-Aldosterone Studies in Special Instructions.

Reference Values: 0-2 years: 4.6 ng/mL/hour (mean)* Range: 1.4-7.8 ng/mL/hour 3-5 years: 2.5 ng/mL/hour (mean)* Range: 1.5-3.5 ng/mL/hour 6-8 years: 1.4 ng/mL/hour (mean)* Range: 0.8-2.0 ng/mL/hour 9-11 years: 1.9 ng/mL/hour (mean)* Range: 0.9-2.9 ng/mL/hour
12-17 years: 1.8 ng/mL/hour (mean) Range: 1.2-2.4 ng/mL/hour
Mean data not standardized as to time of day or diet. Infants were supine, children sitting.

Na-depleted, upright (peripheral vein specimen)
18-39 years: 10.8 ng/mL/hour (mean)
2.9-24.0 ng/mL/hour (range)
> or =40 years: 5.9 ng/mL/hour (mean)
2.9-10.8 ng/mL/hour (range)

Na-replete, upright (peripheral vein specimen)
18-39 years: 1.9 ng/mL/hour (mean)
< or =0.6-4.3 ng/mL/hour (range)
> or =40 years: 1.0 ng/mL/hour (mean)
< or =0.6-3.0 ng/mL/hour (range)


RPTL
9078

Reptilase Time, Plasma

Clinical Information: Prolonged clotting times may be associated with a wide variety of coagulation abnormalities including: -Deficiency or functional abnormality (congenital or acquired) of any of the coagulation proteins -Deficiency or functional abnormality of platelets -Specific factor inhibitors -Acute disseminated intravascular coagulation -Exogenous anticoagulants (eg, heparin, warfarin) The prothrombin time (PT) and activated partial thromboplastin time (APTT) are first-order tests for coagulation abnormalities and are prolonged in many bleeding disorders. A battery of coagulation tests is often required to determine the cause of prolonged clotting times. The thrombin time (TT) test is used to identify the cause of prolonged APTT or dilute Russell's viper venom time (DRVVT). Reptilase time (RT) test is used to evaluate a prolonged TT. Reptilase is a thrombin-like enzyme isolated from the venom of Bothrops atrox. Thrombin splits small fibrinopeptides A and B from fibrinogen molecules, producing fibrin monomer, which polymerizes to form a clot. Reptilase, however, splits off fibrinopeptide A but not B, which results in fibrin polymerization. In contrast to thrombin and the TT test which are inhibited by heparin, the RT is normal in the presence of heparin. Similar to the TT test, the RT is prolonged in the presence of hypofibrinogenemia and dysfibrinogenemia.

Useful For: Evaluation of a prolonged thrombin time (TT): It is mainly used to confirm or exclude the presence of heparin in the specimen or specimen type Evaluating hypofibrinogenemia or dysfibrinogenemia in conjunction with the TT and fibrinogen assay

Interpretation: As seen in the following table, reptilase time can help distinguish among the various causes of a prolonged thrombin time (TT). Thrombin Time Reptilase Time Causes Remarks Prolonged Prolonged Hypo- or afibrinogenemia Ascertain by determination of fibrinogen Prolonged Prolonged Dysfibrinogenemia Ascertain by specific assay Prolonged Normal Heparin or inhibitor of thrombin Differentiate by human TT and/or heparin assays Prolonged Prolonged Fibrin(ogen) split products (FSP) Ascertain by FSP or D-dimer assay

Reference Values:
14-23 seconds

Respiratory Profile, Region 1, North Atlantic (CT, MA, ME, NJ, NH, NY, PA, RI, VT)

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgE may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the North Atlantic region including Connecticut, Maryland, Maine, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

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<tr>
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<th>IgE kU/L</th>
<th>Interpretation</th>
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</thead>
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<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
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<td>4</td>
<td>17.5-49.9</td>
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<td>5</td>
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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
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</table>

Reference values apply to all ages. Total IgE:

Results Reported in kU/L

Age Reference interval
0-5 months < or =13
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<th>Age Range</th>
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<tr>
<td>1 and 2 years</td>
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<tr>
<td>4-6 years</td>
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<tr>
<td>7 and 8 years</td>
<td>&lt; or =403</td>
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<tr>
<td>9-12 years</td>
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<tr>
<td>13-15 years</td>
<td>&lt; or =629</td>
</tr>
<tr>
<td>16 and 17 years</td>
<td>&lt; or =537</td>
</tr>
<tr>
<td>18 years and older</td>
<td>&lt; or =214</td>
</tr>
</tbody>
</table>


**Respiratory Profile, Region 10, Southwestern Grasslands (OK, TX)**

**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Southwestern Grasslands region including Oklahoma and Texas

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.
Reference Values:

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<th>Class IgE kU/L</th>
<th>Interpretation</th>
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</thead>
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<td>Negative</td>
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<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
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<tr>
<td>3</td>
<td>3.50-17.4</td>
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<tr>
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<td>6</td>
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</table>

Reference values apply to all ages. Total IgE:

Results Reported in kU/L

<table>
<thead>
<tr>
<th>Age</th>
<th>Reference interval</th>
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<tr>
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</tbody>
</table>


Respiratory Profile, Region 11, Rocky Mountain (AZ [Mt]; CO; ID [Mt]; NM, UT [Mt]; WY)

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI -bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE
measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Rocky Mountain region including Arizona, Colorado, Idaho, New Mexico, Utah and Wyoming

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

**Reference Values:**

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<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
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<tbody>
<tr>
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</table>

Reference values apply to all ages. Total IgE:

Results Reported in kU/L

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<thead>
<tr>
<th>Age</th>
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<tr>
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</tr>
<tr>
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**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Arid Southwest region including the southern Arizona desert and the southern California desert

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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<tr>
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<tr>
<td>0</td>
<td>Negative</td>
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<tr>
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Reference values apply to all ages. Total IgE:

Results Reported in kU/L

<table>
<thead>
<tr>
<th>Age</th>
<th>Reference interval</th>
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<td>1 and 2 years</td>
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3 years < or =199
4-6 years < or =307
7 and 8 years < or =403
9-12 years < or =696
13-15 years < or =629
16 and 17 years < or =537
18 years and older < or =214


Respiratory Profile, Region 13, Southern Coastal California

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the Southern Coastal California region

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:

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<tr>
<td>4 17.5-49.9</td>
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<td>Strongly positive</td>
</tr>
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</table>

Reference values apply to all ages. Total IgE:

Results Reported in kU/L

<table>
<thead>
<tr>
<th>Age</th>
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Clinical References:
allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in Central California

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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<tbody>
<tr>
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**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Intermountain West region including southern Idaho and Nevada

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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13-15 years  < or =629
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18 years and older  < or =214


Respiratory Profile, Region 16, Inland Northwest (OR, Central and Eastern WA)

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the Inland Northwest region including Oregon and central and east Washington

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:
Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages. Total IgE:

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RPR17  Respiratory Profile, Region 17, Pacific Northwest (Northwestern CA, Western OR, WA)

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI -bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI -bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust
mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Pacific Northwest including the region of Northwestern California, Western Oregon and Washington

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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<td>6</td>
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*Results Reported in kU/L*

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**Respiratory Profile, Region 18, Alaska**

**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes.
The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in Alaska

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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Reference values apply to all ages. Total IgE:

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Respiratory Profile, Region 19, Puerto Rico

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in Puerto Rico

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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**Clinical References:**

**Respiratory Profile, Region 2, Mid-Atlantic (DC, DE, MD, NC, VA)**

**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Mid-Atlantic region including the District of Columbia, Delaware, Maryland, North Carolina and Virginia

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and...
malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

**Reference Values:**

Class IgE kU/L  Interpretation

0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive

Reference values apply to all ages. Total IgE:

Results Reported in kU/L

<table>
<thead>
<tr>
<th>Age</th>
<th>Reference interval</th>
</tr>
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<tbody>
<tr>
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<td>&lt; or =307</td>
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<td>7 and 8 years</td>
<td>&lt; or =403</td>
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<td>&lt; or =696</td>
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</tr>
<tr>
<td>18 years and older</td>
<td>&lt; or =214</td>
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</table>

**Clinical References:**


**Respiratory Profile, Region 3, South Atlantic (GA, N.FA, SC)**

**Clinical Information:**

Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes)
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**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the South Atlantic region including Georgia, Northern Florida and South Carolina.

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<tr>
<td>0</td>
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<td>Negative</td>
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<td>0.35-0.69</td>
<td>Equivocal</td>
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</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
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</table>

Reference values apply to all ages. Total IgE:

Results Reported in kU/L

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<tr>
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<tr>
<td>18 years and older</td>
<td>&lt; or =214</td>
</tr>
</tbody>
</table>

Respiratory Profile, Region 4, Sub-tropic Florida (Florida S. of Orlando)

**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in sub-tropic Florida, which is south of Orlando.

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

**Reference Values:**

<table>
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<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>0</td>
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<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
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</table>

Reference values apply to all ages. Total IgE:

Results Reported in kU/L

<table>
<thead>
<tr>
<th>Age</th>
<th>Reference interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 months</td>
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</table>

Respiratory Profile, Region 5, Ohio Valley (IN, KY, OH, TN, WV)

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the Ohio Valley region including Indiana, Kentucky, Ohio, Tennessee and West Virginia

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

Reference Values:
Class IgE kU/L Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
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6  > or =100  Strongly positive
Reference values apply to all ages.

Total IgE:

Results Reported in kU/L

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<thead>
<tr>
<th>Age</th>
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Respiratory Profile, Region 6, South Central (AL, AR, LA, MS)

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may...
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**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the South Central region including Alabama, Arkansas, Louisiana and Mississippi

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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Results Reported in kU/L

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<th>Age</th>
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**Clinical Information:** Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Northern Midwest region including Michigan, Minnesota, and Wisconsin.

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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<tr>
<th>Class</th>
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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages. Total IgE:</td>
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<td>&lt; or =199</td>
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<td>4-6 years</td>
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Respiratory Profile, Region 8, Central Midwest (IA, IL, MO)

Clinical Information: Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

Useful For: Assessing sensitization to various inhalant allergens commonly found in the Central Midwest region including Iowa, Illinois and Missouri

Interpretation: Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

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<th>Class IgE kU/L</th>
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<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
</tr>
</tbody>
</table>

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Immunoglobulin E (IgE) is one of the 5 classes of immunoglobulins, and is defined by the presence of the epsilon heavy chain. It is the most recently described immunoglobulin, having first been identified in 1966. IgE exists as a monomer, and is present in circulation at very low concentrations, approximately 300-fold lower than that of IgG. The physiologic role of IgE is not well characterized, although it is thought to be involved in defense against parasites, specifically helminthes. The function of IgE is also distinct from other immunoglobulins in that it induces activation of mast cells and basophils through the cell-surface receptor Fc epsilon RI. Fc epsilon RI is a high-affinity receptor specific for IgE present at a high density on tissue-resident mast cells and basophils. Because of this high-affinity interaction, almost all IgE produced by B cells is bound to mast cells or basophils, which explains the low concentration present in circulation. Cross-linking of the Fc epsilon RI-bound IgE leads to cellular activation, resulting in immediate release of preformed granular components (histamine and tryptase) and subsequent production of lipid mediators (prostaglandins and leukotrienes) and cytokines (interleukin-4 and interleukin-5). Elevated concentrations of IgE may occur in the context of allergic disease. However, increases in the amount of circulating IgE can also be found in various other diseases, including primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Total IgE measurements have limited utility for diagnostic evaluation of patients with suspected allergic disease. In this scenario, testing for the presence of allergen-specific IgEs may provide more information. Clinical manifestations of allergic disease result from activation of mast cells and basophils, which occurs when Fc epsilon RI-bound IgE antibodies interact with allergen. In vitro serum testing for specific IgE antibodies may provide an indication of the immune response to an allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. Sensitization to inhalant allergens (dust mite, mold, and pollen inhalants) primarily occurs in older
children, adolescents, and adults, and usually manifests as respiratory disease (rhinitis and asthma).

**Useful For:** Assessing sensitization to various inhalant allergens commonly found in the Great Plains region including Kansas, North Dakota, Nebraska and South Dakota

**Interpretation:** Elevated concentrations of total IgE may be found in a variety of clinical diseases, including allergic disease, certain primary immunodeficiencies, infections, inflammatory diseases, and malignancies. Detection of allergen-specific IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
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<td>0</td>
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<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages. Total IgE:

Results Reported in kU/L

<table>
<thead>
<tr>
<th>Age</th>
<th>Reference interval</th>
</tr>
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<tbody>
<tr>
<td>0-5 months</td>
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<tr>
<td>6-11 months</td>
<td>&lt; or =34</td>
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<tr>
<td>1 and 2 years</td>
<td>&lt; or =97</td>
</tr>
<tr>
<td>3 years</td>
<td>&lt; or =199</td>
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<tr>
<td>4-6 years</td>
<td>&lt; or =307</td>
</tr>
<tr>
<td>7 and 8 years</td>
<td>&lt; or =403</td>
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<td>9-12 years</td>
<td>&lt; or =696</td>
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<tr>
<td>13-15 years</td>
<td>&lt; or =629</td>
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<td>16 and 17 years</td>
<td>&lt; or =537</td>
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<tr>
<td>18 years and older</td>
<td>&lt; or =214</td>
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</tbody>
</table>


**SRSV** 8301

**Respiratory Syncytial Virus (RSV) Antibodies, IgG and IgM (Separate Determinations), Serum**

**Clinical Information:** Respiratory syncytial virus (RSV) is an important cause of human respiratory infection. It strikes most frequently and severely in the very young and is a common cause of bronchiolitis, pneumonia, or croup in young infants. Infections in older children and adults tend to be milder and to involve the upper respiratory tract. RSV infections are seasonal, from late fall to spring, and often occur in epidemic form.
Useful For: Aiding in the diagnosis of a recent respiratory syncytial virus infection Not useful for diagnosis from spinal fluid.

Interpretation: The presence of IgM class antibodies or a 4-fold or greater rise in paired sera IgG titer indicates recent infection. The presence of demonstrable IgG generally indicates past exposure and immunity.

Reference Values:
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

**RET Proto-Oncogene, Full Gene Analysis**

**Clinical Information:** Mutations in the RET proto-oncogene are associated with 3 distinct, and in rare cases, overlapping clinical syndromes. Multiple endocrine neoplasia type 2 (MEN2): MEN2 is an autosomal dominant cancer syndrome that has classically been divided into 3 subtypes: MEN 2A, MEN 2B, and familial medullary thyroid carcinoma (FMTC). The characteristic features of MEN 2A include multifocal medullary thyroid carcinoma (MTC), bilateral pheochromocytoma, and primary hyperparathyroidism. MEN 2B is characterized by MTC, pheochromocytoma, and multiple mucosal neuromas. Other features of MEN 2B include enlarged nerves of the gastrointestinal tract (ganglioneuromatosis), marfanoid habitus, hypotonia, and corneal nerve thickening. FMTC has traditionally been diagnosed in families with 4 or more cases of MTC in the absence of pheochromocytoma or parathyroid involvement. Early diagnosis of thyroid cancer and appropriate surgical intervention can prevent metastatic MTC and can reduce the morbidity and mortality associated with MTC. The majority of MEN2-related mutations occur at conserved cysteine residues within exons 10 and 11. Additional mutations in exons 13, 14, 15, and 16 account for the majority of other MEN2-related RET mutations. Taken together, mutations in these codons account for approximately 98% of MEN 2A, >99% of MEN2B, and 96% of FMTC. Hirschsprung disease (HSCR): HSCR is a congenital disorder of impaired intestinal motility, also known as aganglionic megacolon. Variable lengths of the colon may be affected, resulting in either total aganglionosis, long-segment HSCR, or short-segment HSCR. HSCR affects approximately 1 in 5,000 live births and is resolved via surgical intervention. Although gain of function mutations in RET may result in MEN2, loss of function mutations have been reported in patients with Hirschsprung disease (HSCR). It has been reported that up to 50% of familial cases of HSCR and 3% to 35% of sporadic HSCR are due to RET germline mutations. However, most of the mutations that cause HSCR occur outside of the codons that are typically mutated in MEN2. Congenital central hypoventilation syndrome (CCHS): CCHS is a congenital disorder of autonomic nervous system dysfunction in which individuals hypoventilate during sleep, and less commonly while awake. While not the primary etiology of disease, RET mutations have been associated with CCHS; in addition, RET mutations may be modifiers of CCHS development in individuals with HSCR. Co-occurrence of HSCR and CCHS is more commonly observed than the co-occurrence of MEN2 with either HSCR or CCHS.

**Useful For:** Confirmation of suspected clinical diagnosis of multiple endocrine neoplasia type A or B, Hirschsprung disease, or congenital central hypoventilation syndrome in patients with a suspected diagnosis of any of these conditions Identification of familial RET mutation to allow for predictive or diagnostic testing in family members

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:** An interpretive report will be provided.

Reticulin Antibodies, Serum

**Clinical Information:** Celiac disease (CD) is a genetically inherited autoimmune digestive disease and tends to occur in families of European descent. Family members of people with CD or dermatitis herpetiformis are at increased risk of CD. CD is characterized by a permanent intolerance to gluten. When gluten is ingested, the immune system triggers an isolated inflammatory response in the small intestinal mucosa. A lifetime gluten-free diet can completely stop the immune response. Once the patient is on a gluten-free diet, the small intestine begins to repair itself and the antibody levels decline and eventually disappear. However, reintroduction of gluten-containing products stimulates the immune response again. A significant reduction in morbidity and mortality occurs when patients adhere to the gluten-free diet. Patients with CD produce various autoantibodies, including endomysial (EMA), tissue transglutaminase (tTG), gliadin, and reticulin antibodies, as part of the immune response. IgA antibodies usually predominate although patients may also produce IgG autoantibodies. The levels of these antibodies decline following institution of a gluten-free diet. tTG is the primary autoantigen recognized by EMA antibodies in patients with CD and is currently considered the most useful first level screening test for CD. Reticulin antibodies are no longer considered useful in the diagnosis of CD because they lack the sensitivity and specificity of the EMA and tTG tests. Serological screening offers a minimally invasive option for rapid identification of those likely to have CD and to select those who should be subjected to biopsy. Markedly positive (serologically) individuals are highly likely to have CD and should undergo biopsy to confirm the diagnosis.

**Useful For:** Investigation of celiac disease (CD) Reticulin antibodies are no longer considered useful in the diagnosis of CD. Mayo Medical Laboratories recommends ordering TTGA / Tissue Transglutaminase (tTG) Antibody, IgA, Serum or EMA / Endomysial Antibodies (IgA), Serum for evaluation of patients suspected of CD or dermatitis herpetiformis.

**Interpretation:** Decreasing titers suggest successful avoidance of gluten.

**Reference Values:**
Negative
If positive, results are titered.

Reference values apply to all ages.

**Clinical References:**

Reticulocytes, Blood

**Clinical Information:** Reticulocytes are immature erythrocytes (RBC) that have been released into the peripheral blood from the bone marrow after extrusion of their nucleus. The reticulocyte contains residual polyribosomes used in the formation of hemoglobin in the developing erythrocyte.

**Useful For:** Assessing erythropoietic bone marrow activity in anemia and other hematologic conditions

**Interpretation:** The reticulocyte count is a measure of the number of RBCs delivered by the bone marrow. It is elevated with active erythropoiesis such as regeneration, and is decreased in hypoplastic or deficiency conditions such as vitamin B12 deficiency.

**Reference Values:**
% RETICULOCYTES
1-3 days: 3.47-5.40%
4 days-4 weeks: 1.06-2.37%
5 weeks-7 weeks: 2.12-3.47%
8 weeks-5 months: 1.55-2.70%
6 months-23 months: 0.99-1.82%
24 months-5 years: 0.82-1.45%
6-11 years: 0.98-1.94%
12-17 years: 0.90-1.49%
Adults: 0.60-2.71%

ABSOLUTE RETICULOCYTES
1-3 days: 147.5-216.4 x 10^9/L
4 days-4 weeks: 51.3-110.4 x 10^9/L
5 weeks-7 weeks: 51.8-77.9 x 10^9/L
8 weeks-5 months: 48.2-88.2 x 10^9/L
6 months-23 months: 43.5-111.1 x 10^9/L
24 months-5 years: 36.4-68.0 x 10^9/L
6-11 years: 42.4-70.2 x 10^9/L
12-17 years: 41.6-65.1 x 10^9/L
Adults: 30.4-110.9 x 10^9/L


FREB
90331
Retinol Binding Protein
Reference Values:
1.5 - 6.7 mg/dL

RBP24
81783
Retinol-Binding Protein, 24 Hour, Urine
Clinical Information: Retinol-binding protein is a low-molecular-weight protein of 21 kDa that transports retinol (vitamin A alcohol) from the liver to peripheral tissues. Retinol-binding protein is most often found bound to transthyretin, but a small, unbound fraction (<10%) passes freely through glomerular membranes and is reabsorbed by renal proximal tubules cells where it is catabolized. Due to extensive tubular reabsorption, under normal conditions very little of the filtered retinol-binding protein appears in the final excreted urine. Therefore, an increase in the urinary excretion of retinol-binding protein indicates proximal tubule injury and/or impaired proximal tubular function. Measurement of retinol-binding protein in urine is, therefore, a useful aid in the monitoring and/or diagnosis of kidney disease. Elevated excretion rates can indicate tubular damage associated with renal tubulointerstitial nephritis or tubular toxicity from heavy metal or nephrotoxic drug exposure. Glomerulonephropathies and renal vasculopathies also are often associated with coexisting tubular injury and so may result in elevated retinol-binding protein excretion. Measurement of urinary excretion of alpha-1-microglobulin, another low-molecular-weight protein, is an alternative to the measurement of retinol-binding protein. To date, there are no convincing studies to indicate that one test has better clinical utility than the other. Urinary excretion of retinol-binding protein can be determined from either a 24-hour collection or from a random urine collection. The 24-hour collection is traditionally considered the gold standard. For random or spot collections, the concentration of retinol-binding protein is divided by the urinary creatinine concentration. This corrected value adjusts retinol-binding protein for variabilities in urine concentration.
**Useful For:** Assessing renal tubular injury or dysfunction Screening for other tubular abnormalities Detecting chronic asymptomatic renal tubular dysfunction(2)

**Interpretation:** Retinol-binding protein above the reference values may be indicative of a proximal tubular dysfunction.

**Reference Values:**
<163 mcg/24 hours

**Clinical References:**

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**Retinol-Binding Protein, Random, Urine**

**Clinical Information:** Retinol-binding protein is a low-molecular-weight protein of 21 kDa that transports retinol (vitamin A alcohol) from the liver to peripheral tissues.(1) Retinol-binding protein is most often found bound to transthyretin, but a small, unbound fraction (<10%) passes freely through glomerular membranes and is reabsorbed by renal proximal tubules cells where it is catabolized. Due to extensive tubular reabsorption, under normal conditions very little of the filtered retinol-binding protein appears in the final excreted urine. Therefore, an increase in the urinary excretion of retinol-binding protein indicates proximal tubule injury and/or impaired proximal tubular function.(1) Measurement of retinol-binding protein in urine is, therefore, a useful aid in the monitoring and/or diagnosis of kidney disease. Elevated excretion rates can indicate tubular damage associated with renal tubulointerstitial nephritis or tubular toxicity from heavy metal or nephrotoxic drug exposure. Glomerulonephropathies and renal vasculopathies also are often associated with coexisting tubular injury and so may result in elevated retinol-binding protein excretion. Measurement of urinary excretion of alpha-1-microglobulin, another low-molecular-weight protein, is an alternative to the measurement of retinol-binding protein. To date, there are no convincing studies to indicate that 1 test has better clinical utility than the other. Urinary excretion of retinol-binding protein can be determined from either a 24-hour collection or from a random urine collection. The 24-hour collection is traditionally considered the gold standard. For random or spot collections, the concentration of retinol-binding protein is divided by the urinary creatinine concentration. This corrected value adjusts retinol-binding protein for variabilities in urine concentration.

**Useful For:** Assessing renal tubular injury or dysfunction Screening for other tubular abnormalities Detecting chronic asymptomatic renal tubular dysfunction(2)

**Interpretation:** Retinol-binding protein above the reference values may be indicative of a proximal tubular dysfunction.

**Reference Values:**
<50 years: <130 mcg/g creatinine
> or =50 years: <172 mcg/g creatinine

**Clinical References:**

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**Rhabdomyolysis and Myopathy Panel (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.
**Rheumatoid Factor, Serum**

**Clinical Information:** Rheumatoid factors (RF) are a heterogeneous group of autoantibodies that are associated with the diagnosis of rheumatoid arthritis (RA), but can also be found in other inflammatory rheumatic and nonrheumatic conditions. They can also be detected in some healthy individuals 60 years and older. Despite being nonspecific, the detection of RF or anticitrullinated protein (anti-CCP) antibody, is part of the 2010 diagnosis criterion of the American College of Rheumatology for classification of RA. More than 75% of patients with RA have an IgM antibody to IgG immunoglobulin. The titer of RF correlates poorly with disease activity, but those patients with high titers tend to have more severe disease and, thus, a poorer prognosis than do sero-negative patients. A meta-analysis compared the sensitivity and specificity of IgM RF versus anti-CCP antibody. For IgM RF, the sensitivity was 69% (CI, 65%-73%), and specificity was 85% (CI, 82%-88%). For comparison, the sensitivity for anti-CCP antibody was 67% (95% CI, 62%-72%), and 95% (CI, 94%-97%). Both anti-CCP and RF are useful in the diagnosis of RA, and use of both tests has been shown to increase diagnostic sensitivity.

**Useful For:** Diagnosis and prognosis of rheumatoid arthritis

**Interpretation:** Positive results are consistent with but not specific for, rheumatoid arthritis.

**Reference Values:**

<15 IU/mL

**Clinical References:**


**Rhizopus nigricans, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
### Rhodotorula IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

### Rhubarb (Rheum rhaponticum) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

### Ribavirin, Serum

**Clinical Information:** Ribavirin is a nucleoside analog with antiviral activity against a number of RNA and DNA viruses, including hepatitis C virus (HCV). In combination with interferon, ribavirin is a treatment of choice for chronic HCV infection. In this setting, higher serum concentrations of ribavirin appear to correlate with the likelihood of achieving virological response; however, the drug dose is limited by concentration-dependent hemolytic anemia. Although no consensus therapeutic targets or toxic thresholds have been established, ribavirin concentrations between 2,500 and 4,000 ng/mL have been suggested to improve virological response and minimize toxicity. The half-life of ribavirin is very long, typically 5 days or more. For this reason, steady-state concentrations are not achieved until several weeks into therapy; most studies have performed initial therapeutic monitoring after at least 28 days of ribavirin treatment. Specimens should be drawn immediately prior to the next scheduled dose, or at minimum >12 hours after the last dose. Elimination of ribavirin is also very slow, and due to incorporation of the drug into red blood cells, may take up to 6 months after the cessation of therapy. Ribavirin has shown teratogenic activity in animal models, thus patients are recommended to practice stringent birth control until at least 6 months after the end of treatment.

**Useful For:** Assessing adequacy of ribavirin therapy or potential drug-related toxicity
**Interpretation:** Ribavirin concentrations >2,500 ng/mL appear to correlate with greater likelihood of virological response in patients with chronic hepatitis C virus infection. Elevated concentrations in the setting of hemolytic anemia are consistent with ribavirin toxicity.

**Reference Values:**
2,500-4,000 ng/mL

**Clinical References:**

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**Riboflavin (Vitamin B2), Plasma**

**Clinical Information:** There are 3 principle vitamin B2-active flavins found in nature riboflavin, riboflavin 5-phosphate (flavin mononucleotide: FMN), and riboflavin-5'-adenosyl-diphosphate (flavin adenine dinucleotide: FAD). In biological tissues, FMN and FAD serve as prosthetic units for a large variety of flavoproteins, which are hydrogen carriers in oxidation-reduction processes. Dietary deficiency of riboflavin (ariboflavinosis) is characterized by sore throat, cheilosis (lesions on the lips), angular stomatitis (lesions on the angles of the mouth), glossitis (fissured and magenta-colored tongue), corneal vascularization, dysesthesia (red, scaly, greasy patches on the nose, eyelids, scrotum, and labia), and normocytic, normochromic anemia. Severe riboflavin deficiency may affect the conversion of vitamin B6 to its coenzyme, as well as conversion of tryptophan to niacin. Riboflavin has a low level of toxicity and no case of riboflavin toxicity in humans has been reported. The limited absorptivity of riboflavin and its ready excretion in the urine normally preclude a health problem due to increased intake of riboflavin.

**Useful For:** Evaluation of persons who present the signs of ariboflavinosis

**Interpretation:** Low concentrations in the blood plasma are indicative of nutritional deficiency. Concentrations below 1 mcg/L are considered significantly diminished. Marginally low levels probably represent nutritional deficiency that should be corrected.

**Reference Values:**
Normal: 1-19 mcg/L

**Clinical References:**

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**Ribosome P Antibodies, IgG, Serum**

**Clinical Information:** The 80S mammalian ribosome is composed of approximately equal amounts of protein and RNA. The larger 60S subunit contains 3 acidic phosphoproteins, PO, P1, and P2 with molecular masses of 38 kDa, 19 kDa, and 17 kDa, respectively. The major immunoreactive epitope of these 3 autoantgens is found within 22 consecutive amino acids of the carboxy terminus of these 3 highly
conserved proteins. It has been known for some time that sera from some patients with lupus erythematosus (LE) react with ribosomal protein antigens. Studies performed with synthetic peptide antigens revealed that reactivity detected by immunoprecipitation and by immunofluorescence methods in sera from LE patients was directed at the above mentioned epitope. Antibodies to ribosome P proteins are considered highly specific for LE, and have been reported in patients with central nervous system (CNS) involvement and so called "lupus psychosis." The reported frequency of antibodies to ribosome P protein autoantigens in patients with LE is approximately 12%. Since patients with LE may manifest signs and symptoms of CNS diseases including neuropsychiatric symptoms, the presence of antibodies to ribosome P protein may be useful in the differential diagnosis of such patients. Other causes of CNS symptoms in patients with LE include thrombosis with or without antibodies to phospholipid antigens and iatrogenic effects from treatment with corticosteroid drugs.

**Useful For:** As an adjunct in the evaluation of patients with lupus erythematosus (LE) Aids in the differential diagnosis of neuropsychiatric symptoms in patients with LE

**Interpretation:** A positive result is consistent with the diagnosis of lupus erythematosus, and may indicate the presence of central nervous system involvement.

**Reference Values:**
- <1.0 U (negative)
- >or =1.0 U (positive)

Reference values apply to all ages.


---

**Rice IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
- <2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

---

**Rice, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease
and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**ROMA2**

**Risk Score, if Postmenopausal**

**Reference Values:** Only orderable as part of a profile. For more information see ROMA / Ovarian Malignancy Risk Algorithm.

**ROMA1**

**Risk Score, if Premenopausal**

**Reference Values:** Only orderable as part of a profile. For more information see ROMA / Ovarian Malignancy Risk Algorithm.

**FRISP**

**Risperidone (Risperdal) and 9-Hydroxyrisperidone**

**Reference Values:**

<table>
<thead>
<tr>
<th>Units</th>
<th>ng/mL</th>
</tr>
</thead>
</table>

Expected steady state concentrations of risperidone and 9-hydroxyrisperidone (combined total) in patients receiving recommended daily dosages: 10 - 120 ng/mL.

**RNAP**

**RNA Polymerase III Antibodies, IgG, Serum**

**Clinical Information:** Systemic sclerosis is a multisystem connective tissue (systemic rheumatic) disease characterized by fibroblast dysfunction leading to fibrosis of the skin and internal organs,
microvascular injury leading to tissue hypoxia, and an autoimmune response manifested by production of autoantibodies. The severity of the disease is highly variable among individual patients. Limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis have been recognized as distinct subsets, with worse survival for those with the diffuse form. Clinical features of CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias) can be seen in both limited cutaneous and diffuse cutaneous forms but, overall, are associated with a better prognosis. Several disease-specific and mutually exclusive autoantibodies have been identified that are helpful in both diagnosis and disease classification. Centromere and topoisomerase I (Scl 70) autoantibodies are associated with limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis, respectively. RNA polymerase III is a complex, 16-subunit enzyme directing transcription of small, stable nontranslated RNA genes: tRNAs, 5S rRNA, Alu-RNA and U6 7SK snRNA genes. The immunodominant epitope for autoantibodies with anti-RNA polymerase I/III specificity has been identified on the RNA polymerase-specific subunit RPC155. Autoantibodies to RNA polymerase III antigen are found in 11% to 23% of patients with systemic sclerosis. Systemic sclerosis patients who are positive for RNA polymerase III antibodies form a distinct serologic subgroup and usually do not have any of the other antibodies typically found in systemic sclerosis patients such as anticientromere or anti-Scl70. Numerous studies have shown that systemic sclerosis patients with anti-RNA polymerase III have an increased risk of the diffuse cutaneous form of scleroderma, with a high likelihood of skin involvement and hypertensive renal disease.

**Useful For:** Evaluating patients suspected of having systemic sclerosis, when used in conjunction with centromere and Scl70 antibodies Providing diagnostic and prognostic information in patients with systemic sclerosis

**Interpretation:** A positive result supports a possible diagnosis of systemic sclerosis (see Cautions). This autoantibody is strongly associated with diffuse cutaneous scleroderma and with an increased risk of acute renal crisis. A negative result indicates no detectable IgG antibodies to RNA polymerase III, but does not rule out the possibility of systemic sclerosis (11%-23% sensitivity).

**Reference Values:**
- <20.0 U (negative)
- 20.0-39.9 U (weak positive)
- 40.0-80.0 U (moderate positive)
- >80.0 U (strong positive)

**Clinical References:**

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**RNP Antibodies, IgG, Serum**

**Clinical Information:** RNP (also called nRNP and U1RNP) is a small nuclear ribonucleoprotein that contains 3 protein autoantigens (called A, C, and 68 kD). Sera that contain RNP antibodies react predominately with the A and 68-kD autoantigens. Antibodies to RNP occur in approximately 50% of patients with lupus erythematosus (LE) and in patients with other connective tissue diseases, notably mixed connective tissue disease (MCTD). MCTD is characterized by high levels of RNP antibodies without detectable Sm or double-stranded DNA (dsDNA) antibodies. MCTD resembles LE but is not accompanied by renal involvement. RNP is 1 of 4 autoantigens commonly referred to as extractable nuclear antigens (ENA). The other ENAs are SS-A/Ro, SS-B/La, and Sm. Each ENA is composed of 1 or more proteins associated with small nuclear RNA species (snRNP) ranging in size from 80 to approximately 350 nucleotides. Antibodies to ENAs are common in patients with connective tissue diseases (systemic rheumatic diseases) including LE, MCTD, Sjogren syndrome, scleroderma (systemic sclerosis), and polymyositis/dermatomyositis. See Connective Tissue Disease Cascade
(CTDC) in Special Instructions.

**Useful For:** Evaluating patients with signs and symptoms of a connective tissue disease in whom the test for antinuclear antibodies is positive

**Interpretation:** A positive result for RNP antibodies is consistent with a connective tissue disease. Although strongly associated with connective tissue diseases, RNP antibodies are not considered a “marker” for any particular disease except in the following situation: when found in isolation (ie, dsDNA antibodies and Sm antibodies are not detectable), a positive result for RNP antibodies is consistent with the diagnosis of mixed connective tissue disease.

**Reference Values:**
- <1.0 U (negative)
- ≥1.0 U (positive)

Reference values apply to all ages.

**Clinical References:**

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**ROMA Score (Ovarian Malignancy Risk Algorithm)**

**Clinical Information:** Women with ovarian cancer symptoms and adnexal masses present primarily to gynecologists, primary care physicians or general surgeons. Triage guidelines from the American College of Obstetricians and Gynecologist and the Society of Gynecologic Oncologists recommends referral of women with a pelvic mass at high risk for ovarian cancer to gynecologic oncologists. Specialized treatment improves patient outcomes resulting in fewer complications and better survival rates when compared to patients treated by surgeons less familiar with the management of ovarian cancer. The risk of ovarian malignancy algorithm (ROMA) incorporates cancer antigen 125 (CA125), human epididymal protein 4 (HE4), and menopausal status to assign women that present with an adnexal mass into a high-risk or low-risk group for finding an ovarian malignancy. ROMA is indicated for women who meet the following criteria: older than age 18, presenting with an adnexal mass for which surgery is planned, who have not yet been referred to an oncologist. ROMA must be interpreted in conjunction with clinical and radiological assessment.

**Useful For:** Aids in assessing whether there is a high- or low-likelihood of finding an ovarian malignancy at surgery in women who present with an adnexal mass

**Interpretation:** In premenopausal women, a risk of ovarian malignancy algorithm (ROMA) value equal to or greater than 1.14 indicates a high risk of finding epithelial ovarian cancer, whereas a ROMA value less than 1.14 indicates a low risk of finding epithelial ovarian cancer at surgery. In postmenopausal women, a ROMA value equal to or greater than 2.99 indicates a high risk of finding epithelial ovarian cancer, whereas a ROMA value less than 2.99 indicates a low risk of finding epithelial ovarian cancer at surgery. The use of these cut-points provides a 75% specificity and sensitivity of 84% in patients with stage I-IV epithelial ovarian cancer.

**Reference Values:**
- Females:
  - HE4, S
    - < or =140 pmol/L
  - Cancer Ag 125 (CA 125), S
    - <46 U/mL
  - ROMA Score
    - Premenopausal: <1.14 (low risk)
    - Postmenopausal: <2.99 (low risk)
  - Males: Not applicable
**Clinical References:**

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### FROPI

**57171**

**Ropivacaine, Serum/Plasma**

**Reference Values:**
Reporting limit determined each analysis.

Following epidural administration 10 mg/hr, 20 mg/hr and 30 mg/hr, mean plasma concentration of 0.39, 0.88, 1.19 mcg/mL at 21 hours respectively.

Bolus I.V. administration 84 mg/70 kg and 131 mg/70 kg, peak plasma concentrations of 1.1 and 1.7 mcg/mL at 2 minutes respectively.

### ROTA

**8886**

**Rotavirus Antigen, Feces**

**Clinical Information:** Rotavirus is a major cause of nonbacterial gastroenteritis, especially in infants and very young children (6 months-2 years of age) who have not received the rotavirus vaccine. Infection may be entirely asymptomatic or produce a spectrum of disease ranging from mild gastroenteritis to severe diarrhea and vomiting with dehydration. Infection usually begins acutely and lasts for 4 to 8 days. In temperate climates, rotaviral infections are seasonal; they peak in frequency during the winter months and are uncommon during the summer. Rotaviral gastroenteritis is, therefore, sometimes called "winter vomiting disease." Infection is more likely to be symptomatic in preterm infants, immunosuppressed patients, and elderly individuals, especially those living in nursing homes or other confined quarters. In other children and adults, rotavirus infections are usually subclinical and may be associated with asymptomatic shedding of rotavirus in the feces. Rapid and accurate detection of rotavirus antigens in stool specimens may lead to better patient management, particularly in hospitalized or institutionalized patients.

**Useful For:** Investigation of patients with diarrhea, particularly infants, the elderly, and immunocompromised patients. Investigation of nosocomial diarrhea

**Interpretation:** Peak viral counts are reported to occur on days 3 to 5 after onset of symptoms. The virus is eliminated from the infected individual within a few days following acute infection. Specimens collected 8 days or more after onset of symptoms may not contain enough rotavirus antigen to produce a positive reaction. A prolonged carrier state has been recognized with rotavirus infection. The rate of positive test results may vary due to age, weather, seasonal factors, geographic location, and the general health environment for the group under study. See Laboratory Testing for Infectious Causes of Diarrhea Algorithm in Special Instructions for other diagnostic tests that may be of value in evaluating patients with diarrhea.

**Reference Values:**
Negative


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### MARS

**82701**

**Rough Marsh Elder, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Rough Pigweed, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Identifying allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Rubella Antibodies, IgG, Serum

Clinical Information: Rubella (German or 3-day measles) is a member of the Togavirus family and humans remain the only natural host for this virus. Transmission is typically through inhalation of infectious aerosolized respiratory droplets and the incubation period following exposure can range from 12 to 23 days. (1) Infection is generally mild and self-limited, and is characterized by a maculopapular rash beginning on the face and spreading to the trunk and extremities, fever, malaise, and lymphadenopathy. (2) Primary in utero rubella infections can lead to severe sequelae for the fetus, particularly if infection occurs within the first 4 months of gestation. Congenital rubella syndrome is often associated with hearing loss, cardiovascular and ocular defects. (3) The United States 2-dose measles, mumps, rubella (MMR) vaccination program, which calls for vaccination of all children, leads to seroconversion in 95% of children following the first dose. (1) A total of 4 cases of rubella were reported to the CDC in 2011 without any cases of congenital rubella syndrome. (4) Due to the success of the national vaccination program, rubella is no longer considered endemic in the United States (www.cdc.gov/rubella). However, immunity may wane with age as approximately 80% to 90% of adults will show serologic evidence of immunity to rubella.

Useful For: Determination of immune status to the rubella virus

Interpretation: Positive: Antibody index (AI) value of 1.0 or higher - The reported AI value is for reference only. This is a qualitative test and the numeric value of the AI is not indicative of the amount of antibody present. AI values above the manufacturer recommended cutoff for this assay indicate that specific antibodies were detected, suggesting prior exposure or vaccination. - The presence of detectable IgG-class antibodies indicates immunity to the rubella virus through prior immunization or exposure. Individuals testing positive are considered immune to rubella infection. Equivocal: AI value 0.8-0.9 Submit an additional sample for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative: AI value of 0.7 or lower The absence of detectable IgG-class antibodies suggests the lack of a specific immune response to immunization or no prior exposure to the rubella virus.

Reference Values:

Vaccinated: positive (> or =1.0 AI)
Unvaccinated: negative (< or =0.7 AI)

**Rubeola (Measles) Antibodies, IgG and IgM (Separate Determinations), Spinal Fluid**

**Clinical Information:** Measles is a serious and highly contagious disease that can be a leading cause of death where nutrition and sanitation are limited. Onset begins with cough, fever, and lymphadenopathy approximately 2 weeks after exposure. Diagnosis is usually made when the rash appears. Koplik spots may be seen earlier on the buccal mucosa. Complications of measles may develop in children who appear to have normal immune functions. Persistent infection of the central nervous system with measles virus is recognized to cause the disease subacute sclerosing panencephalitis (SSPE). SSPE is a rare, late complication of measles with an incidence of approximately 1 per 100,000 cases. SSPE is a progressive, usually fatal disease that occurs most often in children between the ages of 5 and 14. The onset is insidious and progressive. The incubation period from acute measles to onset of neurological symptoms varies from several months to many years. One of the most useful diagnostic tests involves the measurement of measles-specific antibodies in the cerebrospinal fluid (CSF) of patients with SSPE. Levels of antibody are significantly elevated in the CSF of SSPE patients compared to those without the disease.

**Useful For:** Diagnosis of central nervous system infection with rubeola (measles) virus and/or subacute sclerosing panencephalitis

**Interpretation:** Detection of organism-specific antibodies in the cerebrospinal fluid (CSF) may suggest central nervous system infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of central nervous system infection. Patients with subacute sclerosing panencephalitis have serum antibody titers which are 10 to 100 times higher than those seen in late convalescent-phase sera. More importantly, there is pronounced local production of oligoclonal measles virus antibodies in the central nervous system.

**Reference Values:**
- IgG: <1:5
- IgM: <1:10

Reference values apply to all ages.

**Clinical References:** Gascon GG: Subacute sclerosing panencephalitis. Semin Pediatr Neurol 1996;3:260-269

**Rufinamide, Serum**

**Clinical Information:** Rufinamide is a new antiepileptic drug (AED) approved by the Food and Drug Administration as add-on treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in children > or =4 years, and for the treatment of focal seizures in adults and adolescents. Its mechanism of action is not completely understood, but it is believed to work by prolonging the inactive state of sodium channels and therefore limiting excessive firing of sodium-dependent action potentials. The most commonly observed side effects are headache, dizziness, fatigue, somnolence, and nausea.

**Useful For:** Monitoring serum rufinamide concentrations, assessing compliance, and adjusting dosage in patients receiving other drugs which interact pharmacokinetically with rufinamide (ie, drugs that induce liver CYP3A4 enzymes) and may be helpful in who are receiving hemodialysis.
Interpretation: The reference interval is broad and represents the concentrations observed to be associated with the greatest drug efficacy without side effects or toxicity.

Reference Values:
5.0-30.0 mcg/mL


RUSS 82681

Russian Thistle, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Establishing the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms Identifying allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive

Reference values apply to all ages.

**Rye Food IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Rye Grass, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>6 &gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**Rye, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms Identifying allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>50.0-99.9</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
</tr>
</tbody>
</table>

**Reference values apply to all ages.**


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**S-100 Immunostain, Technical Component Only**

**Clinical Information:** S-100 expression is seen in cartilaginous tumors, myoepithelial tumors, Schwann cells and neural tumors, Langerhans cell proliferations, benign and malignant melanocytes, clear cell sarcoma, and some carcinomas (particularly of the breast). S-100 staining occurs both in the nucleus and cytoplasm.

**Useful For:** Aids in the identification of various neoplasms

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the

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Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com Page 2007
context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


S-100B Protein, Serum
Reference Values:
0 â€“ 96 ng/L
This assay is performed using the CanAg S100 Enzyme Immunoassay. Results obtained with different assay methods or kits cannot be used interchangeably.

Saccharomyces cerevisiae Antibody, IgA, Serum
Clinical Information: Inflammatory bowel disease (IBD) refers to 2 diseases, ulcerative colitis (UC) and Crohn's disease (CD), that produce inflammation of the large or small intestines.(1) The diagnoses of both diseases are based on clinical features, the results of barium X-rays, colonoscopy, mucosal biopsy histology, and in some cases operative findings and resected bowel pathology and histology. Recently, patients with IBD have been shown to have antibodies in serum that help distinguish between CD and UC.(2) Patients with UC often have measurable neutrophil-specific antibodies, which react with as yet uncharacterized target antigens in human neutrophils; whereas, patients with CD often have measurable antibodies of the IgA and/or IgG isotypes, which react with cell wall mannan of Saccharomyces cerevisiae strain Su 1.

Useful For: Helping clinicians distinguish between ulcerative colitis and Crohn's disease in patients suspected of having inflammatory bowel disease

Interpretation: In IBDP / Inflammatory Bowel Disease Serology Panel, Serum, anti-Saccharomyces cerevisiae antibodies (ASCA) and neutrophil-specific antibodies (NSA) are measured. The finding of NSA with normal levels of IgA and IgG ASCA is consistent with the diagnosis of ulcerative colitis (UC); the finding of negative NSA with elevated IgA and IgG ASCA is consistent with Crohn's disease (CD). NSA are detectable in approximately 50% of patients with UC. Elevated levels of either IgA or IgG ASCA occur in approximately 55% of patients with CD. Approximately 40% of patients with CD have elevated levels of both IgA and IgG ASCA. Employed together, the tests for NSA and ASCA have the following positive predictive values (PPV) for UC and CD, respectively:(2) -NSA-positive with normal levels of IgA and IgG ASCA, PPV of 91% -NSA-negative with elevated levels of IgA and IgG ASCA, PPV of 90%

Reference Values:
Negative: < or =20.0 U

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**GASCA**

**Saccharomyces cerevisiae Antibody, IgG, Serum**

**Clinical Information:** Inflammatory bowel disease (IBD) refers to 2 diseases, ulcerative colitis (UC) and Crohn's disease (CD), which produce inflammation of the large or small intestines. The diagnoses of both diseases are based on clinical features, radiographic findings, colonoscopy, mucosal biopsy histology, and, in some cases, operative findings and resected bowel pathology and histology. Patients with IBD have also been shown to have antibodies in serum that help distinguish between CD and UC.(2) Patients with UC often have measurable neutrophil-specific antibodies (NSA) that react with as yet uncharacterized target antigens in human neutrophils; whereas patients with CD often have measurable antibodies of the IgA and/or IgG isotypes that react with cell wall mannan of Saccharomyces cerevisiae strain Su 1.

**Useful For:** Helping clinicians distinguish between ulcerative colitis and Crohn's disease in patients suspected of having inflammatory bowel disease

**Interpretation:** In IBDP / Inflammatory Bowel Disease Serology Panel, Serum, anti-Saccharomyces cerevisiae antibodies (ASCA) and neutrophil-specific antibodies (NSA) are measured. The finding of NSA with normal levels of IgA and IgG ASCA is consistent with the diagnosis of ulcerative colitis (UC); the finding of negative NSA with elevated IgA and IgG ASCA is consistent with Crohn's disease (CD). NSA are detectable in approximately 50% of patients with UC. Elevated levels of either IgA or IgG ASCA occur in approximately 55% of patients with CD. Elevated levels of both IgA and IgG ASCA occur in approximately 40% of patients with CD. Employed together, the tests for NSA and ASCA have the following positive predictive values (PPV) for UC and CD, respectively:(2) -NSA-positive with normal levels of IgA and IgG ASCA, PPV of 91% -NSA-negative with elevated levels of IgA and IgG ASCA, PPV of 90%

**Reference Values:**

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>&lt; or =20.0 U</td>
</tr>
<tr>
<td>Equivocal</td>
<td>20.1-24.9 U</td>
</tr>
<tr>
<td>Weakly positive</td>
<td>25.0-34.9 U</td>
</tr>
<tr>
<td>Positive</td>
<td>&gt; or =35.0 U</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**FSFLE**

**Safflower (Carthamus tinctorius) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 – 0.69 Low Positive 2 0.70 – 3.49 Moderate Positive 3 3.50 – 17.49 Positive 4 17.50 – 49.99 Strong Positive 5 50.00 – 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L
**Sage (Artemisia spp.) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

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**Sage (Salvia officinalis) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.4 Moderate Positive 3 3.5 â€“ 17.4 High Positive 4 17.5 â€“ 49.9 Very High Positive 5 50.0 â€“ 99.9 Very High Positive 6 >=100 Very High Positive

**Reference Values:**

<0.35 kU/L

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**Salicylate, Serum**

**Clinical Information:** Therapeutic salicylates include, among others, salicylic acid, sodium salicylate, methyl salicylate (oil of wintergreen), and acetylsalicylic acid (aspirin). Aspirin is an analgesic, antipyretic, anti-inflammatory drug contained in a large number of preparations. Aspirin is rapidly hydrolyzed by hepatic and blood esterases to the pharmacologically active intermediate, salicylic acid, which has a dose-dependent serum half-life ranging from 3 to 20 hours. Stimulation of the respiratory center in the central nervous system and uncoupling of oxidative phosphorylation are direct effects of salicylate that lead to many of the toxic symptoms observed in overdose situations. Symptoms of salicylate toxicity can include nausea, vomiting, tinnitus, headache, hyperpnea, confusion, hyperthermia, slurred speech, and convulsions. Acid-base disturbances such as compensated respiratory alkalosis (mild toxicity) and metabolic acidosis with increased anion gap (severe toxicity) are commonplace.

**Useful For:** Assessing toxicity This test is not useful for assessing low-dose aspirin therapy

**Interpretation:** Therapeutic concentrations for antipyretic/analgesic are 3.0 to 10.0 mg/dL, while concentrations between 1.5 and 30 mg/dL are for anti-inflammatory effect and treatment of rheumatic fever. Toxic concentrations are 50.0 mg/dL or higher.

**Reference Values:**

Therapeutic: <30.0 mg/dL
Critical value: > or =50.0 mg/dL


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**SALL4 Immunostain, Technical Component Only**

**Clinical Information:** SALL4 is a zinc-finger transcriptional factor. It is required for the maintenance of embryonic stem cell pluripotency by regulating OCT4 transcription. Staining for SALL4 is useful in distinguishing germ cell tumors from carcinomas, lymphomas, and melanomas.

**Useful For:** Aids in the identification of germ cell tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is
required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


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**FSALG**

**Salmon IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**SALM**

**Salmon, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Establishing the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms Identifying allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

### Salt Grass, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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<th>Class</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Sardine (Pilchard), IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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<td></td>
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<tr>
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<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


SCA 6 (CACNA1A) Repeat Expansion

Reference Values:
A final report will be attached in MayoAccess.

SCA1 (ATXN1) Repeat Expansion

Clinical Information: Detects CAG triplet repeat expansion in the SCA1 gene. Typical Presentation: Ataxia, poor coordination of hand, speech and eye movements, uncoordinated and
unsteady gait.

Reference Values:
A final report will be attached in MayoAccess.

**FSCA3 (MJC/ATXN3) Repeat Expansion**

**Clinical Information:** Hereditary ataxias are a group of heterogeneous neurological disorders predominantly characterized by balance issues, progressive incoordination of gait and limbs, speech and eye movements (2, 3). Additional neurologic and systemic symptoms may be present based on the particular subtype (3). The overall prevalence of hereditary ataxias varies depending on the population but is estimated to be 1-9:100,000 (3). Hereditary ataxias may be broken down into subtypes based on the mode in inheritance. Autosomal dominant ataxias are a clinically diverse group of disorders that consist of spinocerebellar ataxias (SCAs), episodic ataxias (EA), and some complex forms of ataxia (3). Autosomal recessive ataxias are also clinically heterogeneous but typically characterized by areflexia, peripheral sensorimotor neuropathy (often with loss of the sense of proprioception and vibration) and non-neurologic symptoms (2, 3). Repeat expansions of CAG in the ATXN3 gene have been associated with spinocerebellar ataxia-3 (SCA3), also known as Machado Joseph disease (MJD). This disorder is characterized by eye lid retraction and infrequent blinking leading to a “staring eyes” phenotype, ophthalmoparesis, and impaired speech and swallowing (4). Other associated features including peripheral neuropathy, dystonia, and distal amyotrophy with areflexia may be present to varying degrees depending on the size of the repeat length (larger repeats being associated with more severe phenotypes) (4, 5). Age of onset follows an inverse relationship with the number of CAG repeats in the abnormal allele (4). Cases of SCA3 may exhibit anticipation from one generation to the next (4).

Reference Values:
SCA3 CAG Repeat Ranges:
- Normal: $\leq 40$
- Borderline: 41-52
- Positive: $\geq 53$

**Clinical References:**

**SCLE Scale, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

### Reference Values:

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1 0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2 0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3 3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4 17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5 50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6 &gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

### Clinical References:


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**Scallop, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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</tr>
<tr>
<td>4 17.5-49.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


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**SHUR 60451**

**Schistosoma Exam, Urine**

**Clinical Information:** Schistosomiasis is an infection caused by several species of trematodes (flukes) in the genus Schistosoma. The adult worms of Schistosoma haematobium inhabit the venous plexus of the bladder and produce eggs that are typically passed in the urine. Identification of characteristic eggs in urine is diagnostic for infection with this organism.

**Useful For:** As an aid in diagnosing schistosomiasis infections involving the urinary tract

**Interpretation:** A positive result indicates the presence of Schistosoma species ova in urine. A negative result does not rule out the presence of Schistosoma species since ova may be present at levels below the detection limits of this assay, or infection may not involve the urinary tract.

**Reference Values:**
- Negative
- If positive, organism identified


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**BILHA 65019**

**Schistosoma species Antibody, IgG, Serum**

**Clinical Information:** Schistosoma species (class Trematoda) are flukes, characterized by their flat, leaf-like morphology as adults, and use of gastropod molluscs (eg, snails) as an intermediate host. The schistosomes are also referred to as the “blood flukes,” of which there are 5 species known to infect humans: **S mansoni, S japonicum, S haematobium, S mekongi, and S intercalatum.** Among these **S mansoni, S japonicum and S haematobium** are most common. These species have a defined geographic distribution, with **S mansoni** occurring throughout sub-Saharan Africa, the Middle East, and islands in the Caribbean; **S haematobium** found in much of the African continent and the Middle East; and **S japonicum** localized to China, Indonesia, and the Philippines. Humans are definitive hosts for all of the Schistosoma species except for **S japonicum,** and infection begins with skin penetration of cercariae in contaminated water sources. The cercariae shed their bifurcated tails, becoming schistosomulae and migrate through the vascular system to the lungs, heart, and to the portal venous system in the liver. There they mature to adults, pair off and migrate to the mesenteric venules of the bowel and rectum (**S mansoni, S japonicum**) or venus plexus of the bladder (**S haematobium**). **Females will shed eggs, which are moved progressively towards the lumen of the intestine (**S mansoni, S japonicum**) and bladder (**S haematobium**) and are eliminated in the feces or urine, respectively.** These eggs will hatch under ideal conditions, releasing miracidia, which penetrate specific snail (mollusc) intermediate hosts and develop into cercariae, continuing the life cycle. **While many infections are asymptomatic, acute schistosomiasis (Katayama fever) due to **S mansoni** or **S japonicum,** may occur weeks after initial infection. Symptoms include fever, cough, abdominal pain, diarrhea, hepatosplenomegaly, and eosinophilia. Central nervous system infection is uncommon; however, cerebral granulomatous disease may be caused by migration of Schistosoma eggs into the brain or spinal cord.** Cystitis and ureteritis with haematuria are associated with **S haematobium** infection, and can progress to bladder cancer. Diagnosis of schistosomiasis can be made by detection of eggs in stool or urine samples as appropriate for each species. Antibody detection can be useful to in patients who reside in nonendemic areas, but have recently traveled to regions where Schistosoma species are found, and in whom eggs cannot be identified in fecal or urine examinations.

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  Page 2016
**SCL70**

**Scl 70 Antibodies, IgG, Serum**

**Clinical Information:** Scl 70 (topoisomerase 1) is a 100-kD nuclear and nucleolar enzyme. Scl 70 antibodies are considered to be specific for scleroderm (systemic sclerosis) and are found in up to 60% of patients with this connective tissue disease. Scl 70 antibodies are more common in patients with extensive cutaneous involvement and interstitial pulmonary fibrosis, and are considered a poor prognostic sign. (1,2) See Connective Tissue Disease Cascade (CTDC) in Special Instructions.

**Useful For:** Evaluating patients with signs and symptoms of scleroderma and other connective tissue diseases in whom the test for antinuclear antibodies is positive.

**Interpretation:** A positive test result for Scl 70 antibodies is consistent with a diagnosis of scleroderma.

**Reference Values:**

- <1.0 U (negative)
- ≥1.0 U (positive)

Reference values apply to all ages.

**Clinical References:**

**SCN4A (Myotonia) DNA Sequencing Test**

**Reference Values:**

A final report will be attached in MayoAccess.

**SDHBZ**

**SDHB Gene, Full Gene Analysis**

**Clinical Information:** Succinate dehydrogenase (SDH) is a mitochondrial membrane-bound enzyme complex consisting of 4 subunits: SDHA, SDHB, SDHC, and SDHD. SDH is an oxidoreductase that catalyzes the oxidation of succinate to fumarate (tricarboxylic acid cycle function) and the reduction of ubiquinone to ubiquinol (respiratory chain function). Heterozygous pathogenic variants of SDHB, SDHC, or SDHD result in an autosomal dominant tumor syndrome with variable lifetime penetrance. Patients have only 1 functioning germine copy of the affected SDH subunit gene. When the second, intact copy is somatically lost or mutated in target tissues, tumors develop. Tumorigenesis is believed to be mediated through the hypoxia-inducible factor (HIF) pathway, which...
gets activated as a consequence of the loss of function of the enzyme complex. Sympathetic and parasympathetic ganglia are preferentially affected, resulting in development of paragangliomas (PGLs) or pheochromocytomas (PCCs). PGLs might include parasympathetic ganglia (neck and skull-base) or sympathetic ganglia (paravertebral sympathetic chain from neck to pelvis). PCCs can involve 1 or both adrenal glands. Almost all PCCs overproduce catecholamines, resulting in hypertension with a predilection for hypertensive crises. About 20% of PGL, mostly intra-abdominal, also secrete catecholamines. PGLs in the neck usually do not produce catecholamines. SDH-associated PGLs and PCCs are typically not malignant; however, malignancy has been described in a minority of patients (especially in patients with pathogenic SDHB variants). In addition, because of the germline presence of the pathogenic variant, new primary tumors might occur over time in the various target tissues. SDHB is most strongly associated with PGL (usually functioning), but adrenal PCCs also occur, as do occasional gastrointestinal stromal tumors (GIST) and renal cell carcinomas (RCC). The lifetime penetrance of SDHB-related PGL/PCC is relatively low (25%-40%), but approximately half of the clinically affected patients will experience metastatic disease. SDHD shows a disease spectrum similar to SDHB, except head and neck PGLs are more frequent than in SDHB, while functioning or malignant PGLs/PCCs and GISTs are less common. RCCs have thus far not been observed. The lifetime penetrance of paternally transmitted pathogenic SDHD variants is essentially 100%, while maternal transmission of a dysfunctional SDHD copy rarely leads to disease. SDHC has, thus far, been mainly associated with PGLs of skull base and neck. Abdominal and functioning PGLs or PCCs are uncommon, and GISTs are very rare. RCCs have thus far not been observed. However, there is limited certainty about the SDHC genotype-phenotype correlations, as the reported case numbers are low. For the same reason there are no reliable estimates about the lifetime penetrance of SDHC-related PGL/PCC. Collectively, heterozygous germline pathogenic variants of SDHB, SDHC, or SDHD are found in 30% to 50% of apparently sporadic PGL cases, and can be confirmed in approximately 90% of clinically hereditary cases. The corresponding figures are 1% to 25% and 20% to 30% for outwardly sporadic PCC and seemingly inherited PCC, respectively. The prevalence of pathogenic SDHB variants is higher than that of SDHD, which in turn exceeds the numbers for SDHC. SDHB and SDHC show classical autosomal dominant inheritance, while SDHD shows a modified autosomal dominant inheritance with chiefly paternal transmission, suggesting maternal imprinting, the exact molecular correlate of which remains unknown; however, recent evidence suggests tissue-specific distant imprinting that leads to long-range regulation of SDHD expression. A minority of individuals with familial PGL will have pathogenic variants in other genes: SDHAF2 (also known as SDH5), TMEM127, and MAX. Other genes have been described, but need additional study to confirm their clinical relevance and the utility of genetic testing: (i) SDHA variants have been described in familial PCC/PGL; however, all SDHA variants described thus far have been found in patients with seemingly sporadic PCC/PGL, not in familial cases. Moreover, the available data suggests that SDHA variants may have low penetrance and thus clinical utility of genetic testing is difficult to determine. (ii) EGLN1/PHD2, HIF2 alpha, IDH1, and KIF1 beta have also been proposed to predispose to PCC or PGL, but have thus far not been confirmed to do so, or, only do so very rarely. Screening for pathogenic variants in SDH genes is not currently advocated for sporadic PCC, but is gaining in popularity, often alongside tests for mutations of other predisposing genes: SDHAF2, TMEM127, MAX, RET (multiple endocrine neoplasia type 2: MEN2), VHL (von Hippel-Lindau syndrome), NF1 (neurofibromatosis type 1). However, seemingly familial PCC cases that do not have an established diagnosis of a defined familial tumor syndrome, may benefit from SDH gene testing, along with screening of the other predisposing genes previously listed. In order to minimize the cost of genetic testing, the clinical pattern of lesions in PGL and PCC patients may be used to determine the order in which the various predisposing genes listed above should be tested. The latest Endocrine Society Clinical Practice Guideline for pheochromocytoma and paraganglioma (2014) provides the current favored targeted testing approach. Genetic diagnosis of index cases allows targeted presymptomatic testing of relatives.

**Useful For:** Aiding in the diagnosis of hereditary paraganglioma-pheochromocytoma syndrome associated with pathogenic SDHB gene variants

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. (1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly
dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**SDHB Immunostain, Technical Component Only**

**Clinical Information:**
Succinate dehydrogenase B (SDHB) protein is an integral part of the complex II oxidation/reduction pathway. Its function is to transfer electrons from succinate to CoQ. De novo and inheritable mutations in this gene result in paragangliomas and pheochromocytomas. SDHB can be used to differentiate between type 1 (SDHB +) and type 2 (SDHB -) gastrointestinal stromal tumors (GIST). SDHB-deficient GISTs do not respond to imatinib. The cellular localization for SDHB is cytoplasmic and staining is granular (localized to mitochondria). Endothelial cells often stain positive for SDHB and can be used as an internal control when testing GIST tumors.

**Useful For:**
Aids in the identification of succinate dehydrogenase B (SDHB) deficient tumors

**Interpretation:**
This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**SDHB, SDHC, SDHD Gene Panel**

**Clinical Information:**
Succinate dehydrogenase (SDH) is a mitochondrial membrane-bound enzyme complex consisting of 4 subunits: SDHA, SDHB, SDHC, and SDHD. SDH is an oxidoreductase that catalyzes the oxidation of succinate to fumarate (tricarboxylic acid cycle function) and the reduction of ubiquinone to ubiquinol (respiratory chain function). Heterozygous pathogenic
variants of SDHB, SDHC, or SDHD result in an autosomal dominant tumor syndrome with variable lifetime penetrance. Patients have only 1 functioning germline copy of the affected SDH subunit gene. When the second, intact copy is somatically lost or mutated in target tissues, tumors develop. Tumorigenesis is believed to be mediated through the hypoxia-inducible factor (HIF) pathway, which gets activated as a consequence of the loss of function of the enzyme complex. Sympathetic and parasympathetic ganglia are preferentially affected, resulting in development of paragangliomas (PGLs) or pheochromocytomas (PCCs). PGLs might include parasympathetic ganglia (neck and skull-base) or sympathetic ganglia (paravertebral sympathetic chain from neck to pelvis). PCCs can involve 1 or both adrenal glands. Almost all PCCs overproduce catecholamines, resulting in hypertension with a predilection for hypertensive crises. About 20% of PGL, mostly intra-abdominal, also secrete catecholamines. PGLs in the neck usually do not produce catecholamines. SDH-associated PGLs and PCCs are typically not malignant; however, malignancy has been described in a minority of patients (especially in patients with pathogenic SDHB variants). In addition, because of the germline presence of the pathogenic variant, new primary tumors might occur over time in the various target tissues. SDHB is most strongly associated with PGL (usually functioning), but adrenal PCCs also occur, as do occasional gastrointestinal stromal tumors (GIST) and renal cell carcinomas (RCC). The lifetime penetrance of SDHB-related PGL/PCC is relatively low (25%-40%), but approximately half of the clinically affected patients will experience metastatic disease. SDHD shows a disease spectrum similar to SDHB, except head and neck PGLs are more frequent than in SDHB, while functioning or malignant PGLs/PCCs and GISTs are less common. RCCs have thus far not been observed. The lifetime penetrance of paternally transmitted pathogenic SDHD variants is essentially 100%, while maternal transmission of a dysfunctional SDHD copy rarely leads to disease. SDHC has, thus far, been mainly associated with PGLs of skull base and neck. Abdominal and functioning PGLs or PCCs are uncommon, and GISTs are very rare. RCCs have thus far not been observed. However, there is limited certainty about the SDHC genotype-phenotype correlations, as the reported case numbers are low. For the same reason there are no reliable estimates about the lifetime penetrance of SDHC-related PGL/PCC. Collectively, heterozygous germline pathogenic variants of SDHB, SDHC, or SDHD are found in 30% to 50% of apparently sporadic PGL cases, and can be confirmed in approximately 90% of clinically hereditary cases. The corresponding figures are 1% to 25% and 20% to 30% for outwardly sporadic PCC and seemingly inherited PCC, respectively. The prevalence of pathogenic SDHB variants is higher than that of SDHD, which in turn exceeds the numbers for SDHC. SDHB and SDHC show classical autosomal dominant inheritance, while SDHD shows a modified autosomal dominant inheritance with chiefly paternal transmission, suggesting maternal imprinting, the exact molecular correlate of which remains unknown; however, recent evidence suggests tissue-specific distant imprinting that leads to long-range regulation of SDHD expression. A minority of individuals with familial PGL will have pathogenic variants in other genes: SDHAF2 (also known as SDH5), TMEM127, and MAX. Other genes have been described, but need additional study to confirm their clinical relevance and the utility of genetic testing: (i) SDHA variants have been described in familial PCC/PGL; however, all SDHA variants described thus far have been found in patients with seemingly sporadic PCC/PGL, not in familial cases. Moreover, the available data suggests that SDHA variants may have low penetrance and thus clinical utility of genetic testing is difficult to determine. (ii) EGLN1/PHD2, HIF2 alpha, IDH1, and KIF1 beta have also been proposed to predispose to PCC or PGL, but have thus far not been confirmed to do so, or, only do so very rarely. Screening for pathogenic variants in SDH genes is not currently advocated for sporadic PCC, but is gaining in popularity, often alongside tests for mutations of other predisposing genes: SDHAF2, TMEM127, MAX, RET (multiple endocrine neoplasia type 2: MEN2), VHL (von Hippel-Lindau syndrome), NF1 (neurofibromatosis type 1). However, seemingly familial PCC cases that do not have an established diagnosis of a defined familial tumor syndrome, may benefit from SDH gene testing, along with screening of the other predisposing genes previously listed. In order to minimize the cost of genetic testing, the clinical pattern of lesions in PGL and PCC patients may be used to determine the order in which the various predisposing genes listed above should be tested. The latest Endocrine Society Clinical Practice Guideline for pheochromocytoma and paraganglioma (2014) provides the current favored targeted testing approach. Genetic diagnosis of index cases allows targeted pre-symptomatic testing of relatives.

**Useful For:** Aiding in the diagnosis of hereditary paraganglioma-pheochromocytoma syndrome associated with SDHB, SDHC, and SDHD gene mutations

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published
American College of Medical Genetics recommendations as a guideline.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.


**SDHCZ 37443**

**SDHC Gene, Full Gene Analysis**

**Clinical Information:** Succinate dehydrogenase (SDH) is a mitochondrial membrane-bound enzyme complex consisting of 4 subunits: SDHA, SDHB, SDHC, and SDHD. SDH is an oxidoreductase that catalyzes the oxidation of succinate to fumarate (tricarboxylic acid cycle function) and the reduction of ubiquinone to ubiquinol (respiratory chain function). Heterozygous pathogenic variants of SDHB, SDHC, or SDHD result in an autosomal dominant tumor syndrome with variable lifetime penetrance. Patients have only 1 functioning germline copy of the affected SDH subunit gene. When the second, intact copy is somatically lost or mutated in target tissues, tumors develop. Tumorigenesis is believed to be mediated through the hypoxia-inducible factor (HIF) pathway, which gets activated as a consequence of the loss of function of the enzyme complex. Sympathetic and parasympathetic ganglia are preferentially affected, resulting in development of paragangliomas (PGLs) or pheochromocytomas (PCCs). PGLs might include parasympathetic ganglia (neck and skull-base) or sympathetic ganglia (paravertebral sympathetic chain from neck to pelvis). PCCs can involve 1 or both adrenal glands. Almost all PCCs overproduce catecholamines, resulting in hypertension with a predilection for hypertensive crises. About 20% of PGL, mostly intra-abdominal, also secrete catecholamines. PGLs in the neck usually do not produce catecholamines. SDH-associated PGLs and PCCs are typically not malignant; however, malignancy has been described in a minority of patients (especially in patients with pathogenic SDHB variants). In addition, because of the germline presence of the pathogenic variant, new primary tumors might occur over time in the various target tissues. SDHB is most strongly associated with PGL (usually functioning), but adrenal PCCs also occur, as do occasional gastrointestinal stromal tumors (GIST) and renal cell carcinomas (RCC). The lifetime penetrance of SDHB-related PGL/PCC is relatively low (25%-40%), but approximately half of the clinically affected patients will experience metastatic disease. SDHD shows a disease spectrum similar to SDHB, except head and neck PGLs are more frequent than in SDHB, while functioning or malignant PGLs/PCCs and GISTs are less common. RCCs have thus far not been observed. The lifetime penetrance of paternally transmitted pathogenic SDHD variants is essentially 100%, while maternal transmission of a dysfunctional SDH copy rarely leads to disease. SDHC has, thus far, been mainly associated with PGLs of skull base and neck. Abdominal and functioning PGLs or PCCs are uncommon, and GISTs are very rare. RCCs have thus far not been observed. However, there is limited certainty about the SDHC genotype-phenotype correlations, as the reported case numbers are low. For the same reason there are no reliable estimates about the lifetime penetrance of SDHC-related PGL/PCC. Collectively, heterozygous germline pathogenic variants of SDHB, SDHC, or SDHD are found in 30% to 50% of apparently sporadic PGL cases, and can be confirmed in approximately 90% of clinically hereditary cases. The corresponding figures are 1% to 25% and 20% to 30% for outwardly sporadic PCC and
seemingly inherited PCC, respectively. The prevalence of pathogenic SDHB variants is higher than that of SDHD, which in turn exceeds the numbers for SDHC. SDHB and SDHC show classical autosomal dominant inheritance, while SDHD shows a modified autosomal dominant inheritance with chiefly paternal transmission, suggesting maternal imprinting, the exact molecular correlate of which remains unknown; however, recent evidence suggests tissue-specific distant imprinting that leads to long-range regulation of SDHD expression. A minority of individuals with familial PGL will have pathogenic variants in other genes: SDHAF2 (also known as SDH5), TMEM127, and MAX. Other genes have been described, but need additional study to confirm their clinical relevance and the utility of genetic testing: (i) SDHA variants have been described in familial PCC/PGL; however, all SDHA variants described thus far have been found in patients with seemingly sporadic PCC/PGL, not in familial cases. Moreover, the available data suggests that SDHA variants may have low penetrance and thus clinical utility of genetic testing is difficult to determine. (ii) EGLN1/PHD2, HIF2 alpha, IDH1, and KIF1 beta have also been proposed to predispose to PCC or PGL, but have thus far not been confirmed to do so, or, only do so very rarely. Screening for pathogenic variants in SDH genes is not currently advocated for sporadic PCC, but is gaining in popularity, often alongside tests for mutations of other predisposing genes: SDHAF2, TMEM127, MAX, RET (multiple endocrine neoplasia type 2: MEN2), VHL (von Hippel-Lindau syndrome), NF1 (neurofibromatosis type 1). However, seemingly familial PCC cases that do not have an established diagnosis of a defined familial tumor syndrome, may benefit from SDH gene testing, along with screening of the other predisposing genes previously listed. In order to minimize the cost of genetic testing, the clinical pattern of lesions in PGL and PCC patients may be used to determine the order in which the various predisposing genes listed above should be tested. The latest Endocrine Society Clinical Practice Guideline for pheochromocytoma and paraganglioma (2014) provides the current favored targeted testing approach. Genetic diagnosis of index cases allows targeted pre-symptomatic testing of relatives.

**Useful For:** Aiding in the diagnosis of hereditary paraganglioma-pheochromocytoma syndrome associated with pathogenic SDHC gene variants

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. (1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
have only 1 functioning germline copy of the affected SDH subunit gene. When the second, intact copy is somatically lost or mutated in target tissues, tumors develop. Tumorigenesis is believed to be mediated through the hypoxia-inducible factor (HIF) pathway, which gets activated as a consequence of the loss of function of the enzyme complex. Sympathetic and parasympathetic ganglia are preferentially affected, resulting in development of paragangliomas (PGLs) or pheochromocytomas (PCCs). PGLs might include parasympathetic ganglia (neck and skull-base) or sympathetic ganglia (paravertebral sympathetic chain from neck to pelvis). PCCs can involve 1 or both adrenal glands. Almost all PCCs overproduce catecholamines, resulting in hypertension with a predilection for hypertensive crises. About 20% of PGL, mostly intra-abdominal, also secrete catecholamines. PGLs in the neck usually do not produce catecholamines. 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In order to minimize the cost of genetic testing, the clinical pattern of lesions in PGL and PCC patients may be used to determine the order in which the various predisposing genes listed above should be tested. The latest Endocrine Society Clinical Practice Guideline for pheochromocytoma and paraganglioma (2014) provides the current favored targeted testing approach. Genetic diagnosis of index cases allows targeted pre-symptomatic testing of relatives.

**Useful For:** Aiding in the diagnosis of hereditary paraganglioma-pheochromocytoma syndrome associated with pathogenic SDHD gene variants

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments.
detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values:
An interpretive report will be provided.


Seafood Allergen Profile

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com

Seasonal Inhalants Allergen Profile

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class IgE kU/L  Interpretation
0      Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.


Secobarbital, Serum

Clinical Information: Secobarbital is a short-acting barbiturate with hypnotic properties used as a preanesthetic agent and in the short-term treatment of insomnia.(1,2) Secobarbital is administered...
orally. The duration of its hypnotic effect is about 3 to 4 hours. The drug distributes throughout the body, with a volume of distribution (Vd) of 1.6 to 1.9 L/kg, and about 46% to 70% of a dose is bound to plasma proteins. Metabolism takes place in the liver primarily via hepatic microsomal enzymes. Secobarbital's half-life is about 15 to 40 hours (mean: 28 hours).(2,3)

**Useful For:** Monitoring secobarbital therapy

**Interpretation:** Secobarbital concentrations above 5 mcg/mL have been associated with toxicity.

**Reference Values:**
Therapeutic concentration: 1.0-2.0 mcg/mL  
Toxic concentration: >5.0 mcg/mL


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**Secretin**

**Clinical Information:** Secretin is a 27 amino acid basic peptide produced by S cells and released by acid delivered into the duodenum. Secretin is released into the blood when duodenal pH drops below 4. Secretin shares structural similarity with Glucagon, Gastric Inhibitory Polypeptide, Vasoactive Intestinal Polypeptide, PHIM, and Growth Hormone- Releasing Hormone. Secretin is a potent stimulus for bicarbonate secretion. Secretin also stimulates secretion of bile, release of Insulin, and release of Gastric Pepsin in the stomach. Secretin inhibits Glucagon release, intestinal motility, and prevents the uptake of water and sodium ions by the intestine. In normal patients, Secretin has little effect on Gastrin levels, but stimulates Gastrin greatly in Zollinger-Ellison patients. Secretin is also elevated in Zollinger-Ellison patients and in patients with duodenal ulcer. Secretin levels are low in patients with pernicious anemia and achlorhydria. Secretin secretion can be suppressed by Somatostatin, Cimetidine, and Methionine-Enkephalin.

**Reference Values:**
12 - 75 pg/mL (mean=25)

This test was developed and its performance characteristics determined by Inter Science Institute. It has not been cleared or approved by the US Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

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**Sedative Hypnotic Panel, Urine-Forensic**

**Reference Values:**
The following threshold concentrations are used for this analysis.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Screening Threshold</th>
<th>Confirmation Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl Alcohol</td>
<td>0.020 gm/dL</td>
<td>0.020 gm/dL</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>300 ng/mL</td>
<td>100 ng/mL</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>100 ng/mL</td>
<td>75 ng/mL</td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>100 ng/mL</td>
<td>300 ng/mL</td>
</tr>
</tbody>
</table>

Ketamine: Negative  
Screening threshold: 100 ng/mL

Gamma-Hydroxybutyric Acid (GHB): Negative  
Screening threshold: 5.0 ug/mL

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Selenium, Blood

Clinical Information: Plasma and serum typically contain approximately 75% of the selenium measured in whole blood. Selenium whole blood concentrations can be used to assess tissue stores. For routine assessment of selenium deficiency or toxicity, the preferred test is selenium urine.

Useful For: Assessment of tissue stores of selenium

Interpretation: Ultimately, any metal ion concentration value needs to be interpreted in relation to the overall clinical scenario including symptoms, physical findings, and other diagnostic results when determining further actions.

Reference Values:
0-17 years: not established
> or =18 years: 150-241 ng/mL


Selenium, Serum

Clinical Information: Selenium is an essential element. It is a cofactor required to maintain activity of glutathione peroxidase (GSH-Px), an enzyme that catalyzes the degradation of organic hydroperoxides. The absence of selenium correlates with loss of GSH-Px activity and is associated with damage to cell membranes due to accumulation of free radicals. The normal daily dietary intake of selenium is 0.01 to 0.04 parts per million (ppm), which is similar to the typical content of soil (0.05 ppm) and sea water (0.09 ppm). Selenium is found in many over-the-counter vitamin preparations because its antioxidant activity is thought to be anticarcinogenic. There is no supporting evidence that selenium suppresses cancer. In humans, cardiac muscle is the most susceptible to selenium deficiency. With cell membrane damage, normal cells are replaced by fibroblasts. This condition is known as cardiomyopathy and is characterized by an enlarged heart whose muscle is largely replaced by fibrous tissue. In the United States, selenium deficiency is related to use of total parenteral nutrition. This is therapy administered to patients with no functional bowel, such as after surgical removal of the small and large intestine because of cancer, or because of acute inflammatory bowel disease such as Crohn's disease. Selenium supplementation to raise serum concentration above 70 ng/mL is the usual treatment. Serum monitoring done on a semiannual basis checks the adequacy of supplementation. Selenium toxicity has been observed in animals when daily intake exceeds 4 ppm. Teratogenic effects are frequently noted in the offspring of animals living in regions where soil content is high in selenium such as south-central South Dakota and northern-coastal regions of California. Selenium toxicity in humans is not known to be a significant problem except in acute overdose cases. Selenium is not classified as a human teratogen.

Useful For: Monitoring selenium replacement therapy

Interpretation: Selenium accumulates in biological tissue. The normal concentration in adult human blood serum is 70 to 150 ng/mL (0.15 parts per million) with a population mean value of 98 ng/mL. Optimal selenium concentration is age dependent (see Reference Values); children require less circulating selenium than do adults. In the state of selenium deficiency associated with loss of glutathione peroxidase activity, the serum concentration is usually below 40 ng/mL.

Reference Values:
0-2 months: 45-90 ng/mL
3-6 months: 50-120 ng/mL
7-9 months: 60-120 ng/mL
10-12 months: 70-130 ng/mL
> 1 year: 70-150 ng/mL

Effect of micronutrient supplementation on mood in nursing home residents. Gerontology

Semen Analysis

Clinical Information: Semen is composed of spermatozoa suspended in seminal fluid (plasma). The function of the seminal fluid is to provide nutrition and volume for conveying the spermatozoa to the endocervical mucus. Male infertility can be affected by a number of causes. Chief among these is a decrease in the number of viable sperm. Other causes include sperm with abnormal morphology and abnormalities of the seminal fluid.

Useful For: Determining male fertility status

Interpretation: Semen specimens can vary widely in the same man from specimen to specimen. Semen parameters falling outside of the normal ranges do not preclude fertility for that individual. Multiple samples may need to be analyzed prior to establishing patient's fertility status.

Reference Values:
Appearance: normal
Volume: > or =1.5 mL
pH: > or =7.2
Motile/mL: > or =6.0 x 10(6)
Sperm/mL: > or =15.0 x 10(6)
Motility: > or =40%
Grade: > or =2.5

Note: Multiple laboratory studies have indicated that semen parameters for motility and grade on average retain 80% of original parameters when our shipping method is used for transport. Using these averages, samples with 32% to 39% motility and grade of 2 may be in the normal range if testing was performed shortly after collection. Therefore, these borderline patients may need to collect another sample at a local fertility center to verify fertility status. Motile/ejaculate: > or =9.0 x 10(6)
Viscosity: > or =3.0
Agglutination: > or =3.0
Supravital: > or =58% live
Fructose: positive

Note: Fructose testing cannot be performed on semen analysis specimens shipped through Mayo Medical Laboratories. If patient is azoospermic, refer to FROS / Fructose, Semen or Seminal Plasma. Submit separate specimen to rule out ejaculatory duct blockage. Positive result indicates no blockage.


Semen Analysis with Strict Morphology

Clinical Information: Infertility affects 1 out of 6 couples of child-bearing age. Approximately 40% of infertility has a female-factor cause and 40% a male-factor cause. The remaining 20% of infertility is due to a combination of male- and female-factor disorders or is unexplained. Semen is composed of spermatozoa suspended in seminal fluid (plasma). The function of the seminal fluid is to provide nutrition and volume for conveying the spermatozoa to the endocervical mucus. Male infertility can be affected by a number of causes. Chief among these is a decrease in the number of viable sperm. Other causes include sperm with abnormal morphology and abnormalities of the seminal fluid. One of the more successful treatments for male and female infertility is in vitro fertilization (IVF). Male partners are tested with the strict criteria sperm morphology test prior to IVF to assist in the diagnosis of male-factor defects.
Abnormalities in sperm morphology are related to: defects in sperm transport, sperm capacitation, the acrosome reaction, binding and penetration of the zona pellucida, and fusion with the oocyte vitelline membrane. All of these steps are essential to normal fertility. Strict criteria sperm morphology testing also greatly assists with selecting the most cost-effective in vitro sperm processing and insemination treatment for the couple’s IVF cycle. Sperm with severe head abnormalities are unlikely to bind to the zona pellucida. These patients may require intracytoplasmic sperm injection in association with their IVF cycle to ensure optimal levels of fertilization are achieved. This, in turn, provides the patient with the best chance of pregnancy. Multiple semen analyses are usually conducted over the course of the spermatogenic cycle (approximately 70 days).

**Useful For:** Determining male fertility status Selecting the most cost-effective therapy for treating male-factor infertility Quantifying the number of germinal and WBCs per mL of semen

**Interpretation:** Semen specimens can vary widely in the same man from specimen to specimen. Semen parameters falling outside of the normal ranges do not preclude fertility for that individual. Multiple samples may need to be analyzed prior to establishing patient’s fertility status. Sperm are categorized according to strict criteria based on measurements of head and tail sizes and shapes. Sperm with abnormalities in head/tail size/shape may not be capable of completing critical steps in sperm transport and fertilization.

**Reference Values:**

**SEMEN ANALYSIS**
- Appearance: normal
- Volume: $\geq 1.5$ mL
- pH: $\geq 7.2$
- Motile/mL: $\geq 6.0 \times 10^6$
- Sperm/mL: $\geq 15.0 \times 10^6$
- Motility: $\geq 40$
- Grade: $\geq 2.5$

Note: Multiple laboratory studies have indicated that semen parameters for motility and grade on average retain 80% of original parameters when our shipping method is used for transport. Using these averages, samples with 32% to 39% motility and grade of 2 may be in the normal range if testing was performed shortly after collection. Therefore, these borderline patients may need to collect another sample at a local fertility center to verify fertility status
- Motile/ejaculate: $\geq 9.0 \times 10^6$
- Viscosity: $\geq 3.0$
- Agglutination: $\geq 3.0$
- Supravital: $\geq 58$% live
- Fructose: positive

Note: Fructose testing cannot be performed on semen analysis specimens shipped through Mayo Medical Laboratories. If patient is azoospermic, refer to FROS / Fructose, Semen or Seminal Plasma. Submit separate specimen to rule-out ejaculatory duct blockage. Positive result indicates no blockage.

**STRICT MORPHOLOGY**
- Normal forms: $\geq 4.0$% normal oval sperm heads
- Germ cells: $< 4 \times 10^6$ (normal)
  - $\geq 4 \times 10^6$/mL (elevated germinal cells in semen are of unknown clinical significance)
- WBC: $< 1 \times 10^6$ (normal)
  - $\geq 1 \times 10^6$/mL (elevated white blood cells in semen are of questionable clinical significance)


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**SMFL**

**82858**

**Seminal Fluid, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from
immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


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**MIC**

**Sensitivity, MIC (Bill Only)**

**Reference Values:**

This test is for billing purposes only.

This is not an orderable test.

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**SEPTZ**

**SEPT9 Gene, Mutation Screen**

**Clinical Information:** Hereditary neuralgic amyotrophy (HNA) is an autosomal dominant disorder characterized by periods of severe pain involving the brachial plexus followed by muscle atrophy and weakness. These recurrent episodes can also be accompanied by decreased sensation and paresthesias. Individuals with this disease are generally symptom-free between pain attacks, though many experience lingering effects with repeated attacks. The pain episodes are frequently triggered by physical, emotional, or immunological stress. Less commonly, affected individuals can exhibit nonneurological features including short stature, skin folds, hypotelorism, and cleft palate. Mutations in the SEPT9 gene cause the clinical manifestations of HNA. There are 3 common mutations that have been reported in affected
individuals: c.-134G->C, p.R88W, and p.S93F. Additionally, a common exonic duplication attributed to the founder effect has been identified in North American HNA families. Other private duplications of varying sizes have also been identified in affected individuals. SEPT9 is currently the only known gene associated with HNA, although approximately 15% of HNA families do not show linkage to this gene.

**Useful For:** Confirmation of a diagnosis of hereditary neuralgic amyotrophy

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Sequential Maternal Screening, Part 1, Serum**

**Clinical Information:** Maternal serum screening has historically been used in obstetric care to identify pregnancies that may have an increased risk for certain birth defects, such as Down syndrome and trisomy 18. Screening in the second trimester has been available in some version (ie, alpha fetoprotein [AFP] test, triple screen, quad screen) for decades. Screening in the first trimester became an established alternative over the last decade. More recently, sequential screening, which has an improved detection rate as compared to either first- or second-trimester screening, has become a standard option. Sequential screening has a higher detection rate because information about a pregnancy is collected in both trimesters, which provides a greater opportunity for detecting problems. Sequential Maternal Screening, Part 1, Serum involves an ultrasound and a blood draw. The ultrasound measurement is of the back of the fetal neck, where fluid tends to accumulate in babies who have chromosome conditions, heart conditions, and other health problems. This measurement, referred to as the nuchal translucency (NT), is difficult to perform accurately. Therefore, NT data is accepted only from NT-certified sonographers. Along with the NT measurement, a maternal serum specimen is drawn and 1 pregnancy-related marker is measured (pregnancy-associated plasma protein A: PAPP-A). The results of the ultrasound measurement and blood work are then entered, along with the maternal age and demographic information, into a mathematical model that calculates Down syndrome and trisomy 18 risk estimates. If the result from the first-trimester Sequential Maternal Screening, Part 1, Serum indicates a risk for Down syndrome that is higher than the screen cutoff, the screen is completed and a report is issued. In that event, the patient is typically offered counseling and diagnostic testing (ie, either chorionic villus sampling or amniocentesis). When the screen is completed after Sequential Maternal Screen Part 1, a neural tube defect (NTD) risk is not provided. For a stand-alone NTD-risk assessment, order MAFP / Alpha-Fetoprotein (AFP), Single Marker Screen, Maternal, Serum. If the risk from the first trimester is below the established cutoff, an additional serum specimen is drawn in the second trimester for Sequential Maternal Screen, Part 2, which includes tests for AFP, unconjugated estriol (uE3), human chorionic gonadotropin (hCG), and inhibin A. Once that specimen is processed, information from both trimesters is combined and a report is issued. If results are positive, the patient is typically offered counseling and diagnostic testing (ie, amniocentesis). Nuchal Translucency (NT): The NT measurement, an ultrasound marker, is obtained by measuring the fluid-filled space within the nuchal region (back of the neck) of the fetus. While fetal NT measurements obtained by ultrasonography increase in normal pregnancies with advancing gestational age, fetuses with Down syndrome have larger NT measurements than gestational age-matched normal fetuses. Increased fetal
NT measurements can, therefore, serve as an indicator of an increased risk for Down syndrome. Pregnancy-Associated Plasma Protein A (PAPP-A): PAPP-A is a 187-kDA protein comprised of 4 subunits: 2 PAPP-A subunits and 2 pro-major basic protein (proMBP) subunits. PAPP-A is a metalloproteinase that cleaves insulin-like growth factor-binding protein-4 (IGFBP-4), dramatically reducing IGFBP-4 affinity for IGF1 and IGF2, thereby regulating the availability of these growth factors at the tissue level. PAPP-A is highly expressed in first-trimester trophoblasts, participating in regulation of fetal growth. Levels in maternal serum increase throughout pregnancy. Low PAPP-A levels before the fourteenth week of gestation are associated with an increased risk for Down syndrome and trisomy 18.

**Useful For:** Prenatal screening for Down syndrome and trisomy 18
Prenatal screening for neural tube defects (this is only applicable to Part 2 [second trimester] of the test)

**Interpretation:** Maternal screens provide an estimation of risk, not a diagnosis. A negative result indicates that the estimated risk falls below the screen cutoff. A positive result indicates that the estimated risk exceeds the screen cutoff. Down Syndrome: Sequential Maternal Screening, Part 1, Serum results are negative when the calculated risk is below 1/50 (2%). If Part 1 is negative, submit an additional specimen in the second trimester (order SEQF / Sequential Maternal Screening, Part 2, Serum). Sequential Maternal Screening, Part 2, Serum results are negative when the calculated risk is below 1/270 (0.37%). Negative results mean that the risk is less than the established cutoff; they do not guarantee the absence of Down syndrome. Results are positive when the risk is greater than the established cutoff (ie., > or =1/50 in Sequential Maternal Screening, Part 1, Serum and > or =1/270 in Sequential Maternal Screening, Part 2, Serum). Positive results are not diagnostic. When both Sequential Maternal Screening Part 1 and Part 2 are performed with a screen cutoff of 1/270, the combination of maternal age, nuchal translucency (NT), pregnancy-associated plasma protein A (PAPP-A), alpha-fetoprotein (AFP), unconjugated estriol (uE3), human chorionic gonadotropin (hCG), and inhibin A has an overall detection rate of approximately 90% with a false-positive rate of approximately 3% to 4%. In practice, both the detection rate and false-positive rate vary with maternal age. Trisomy 18: In Part 1, trisomy 18 results are only reported if the Down syndrome risk is positive. In Part 2, the screen cutoff for trisomy 18 is 1 in 100 (1%). Risks that are > or =1% are screen-positive; positive results are not diagnostic. Risks <1% are screen-negative; negative results do not guarantee the absence of trisomy 18. Use caution when revising positive results with earlier dating. Babies with trisomy 18 tend to be small, which can lead to underestimation of gestational age and an increased chance of missing a true-positive. When both Sequential Maternal Screening Part 1 and Part 2 of sequential screening are performed with a screen cutoff of 1/100, the combination of maternal age, PAPP-A, AFP, uE3, and hCG has an overall detection rate of approximately 90% with a false-positive rate of approximately 0.1%. Neural Tube Defect (NTD): Risk assessment for NTD is only available after completion of Part 2 of the sequential maternal screen. See SEQF / Sequential Maternal Screening, Part 2, Serum for details. Follow-up: Verify that all information used in the risk calculation is correct (maternal date of birth, gestational dating, etc). If any information is erroneous, contact the laboratory for a revision. Screen-negative results typically do not warrant further evaluation. If the results are positive, the patient is typically offered counseling, ultrasound, diagnostic testing, and possibly, referral to genetics counseling or a high-risk clinic.

**Reference Values:**
An interpretive report will be provided. See Interpretation section for more details.

**Clinical Information:** Maternal serum screening has historically been used in obstetric care to identify pregnancies that may have an increased risk for certain birth defects, such as Down syndrome and trisomy 18. Screening in the second trimester has been available in some version (e.g., alpha fetoprotein [AFP] test, triple screen, quad screen) for decades. Screening in the first trimester began an established alternative over the last decade. More recently, sequential screening, which has an improved detection rate as compared to either first- or second-trimester screening, has become a standard option. Sequential screening has a higher detection rate because information about a pregnancy is collected in both trimesters, which provides a greater opportunity for detecting problems. Sequential Maternal Screening, Part 1, Serum involves an ultrasound and a blood draw. The ultrasound measurement is of the back of the fetal neck, where fluid tends to accumulate in babies who have chromosome conditions, heart conditions, and other health problems. This measurement, referred to as the nuchal translucency (NT), is difficult to perform accurately. Therefore, NT data is accepted only from NT-certified sonographers. Along with the NT measurement, a maternal serum specimen is drawn and 1 pregnancy-related marker is measured (pregnancy-associated plasma protein A: PAPP-A). The results of the ultrasound measurement and blood work are then entered with the maternal age and demographic information into a mathematical model that calculates Down syndrome and trisomy 18 risk estimates. If the result from Part 1 indicates a risk for Down syndrome that is higher than the screen cutoff, the screen is completed and a report is issued. In that event, the patient is typically offered counseling and diagnostic testing (either chorionic villus sampling or amniocentesis). When the screen is completed after Sequential Maternal Screening Part 1, Serum, a neural tube defect (NTD) risk is not provided. For a stand-alone NTD-risk assessment, order MAFP / Alpha-Fetoprotein (AFP), Single Marker Screen, Maternal, Serum. If the risk from the first trimester is below the established cutoff, an additional serum specimen is drawn in the second trimester for Sequential Maternal Screening, Part 2, Serum. Once that specimen is processed, information from both trimesters is combined and a report is issued. If results are positive, the patient is typically offered counseling and diagnostic testing (ie, amniocentesis). Alpha-Fetoprotein (AFP): AFP is a fetal protein that is initially produced in the fetal yolk sac and liver. A small amount also is produced by the gastrointestinal tract. By the end of the first trimester, nearly all of the AFP is produced by the fetal liver. The concentration of AFP peaks in fetal serum between 10 to 13 weeks. Fetal AFP diffuses across the placental barrier into the maternal circulation. A small amount also is transported from the amniotic cavity. The AFP concentration in maternal serum rises throughout pregnancy, from a nonpregnancy level of 0.2 to about 250 ng/mL at 32-weeks gestation. If the fetus has an open neural tube defect (NTD), AFP is thought to leak directly into the amniotic fluid causing high concentrations of AFP. Subsequently, the AFP reaches the maternal circulation, thus producing elevated serum levels. Other fetal abnormalities such as omphalocele, gastroschisis, congenital renal disease, esophageal atresia, and other fetal-distress situations such as threatened abortion and fetal demise, also may show AFP elevations. Increased maternal serum AFP values also may be seen in multiple pregnancies and in unaffected singleton pregnancies in which the gestational age has been underestimated. Lower values have been associated with an increased risk for genetic conditions such as trisomy 21 (Down syndrome) and trisomy 18. Unconjugated Estriol (uE3): Estriol, the principal circulatory estrogen hormone in the blood during pregnancy, is synthesized by the intact feto-placental unit. Estriol exists in maternal blood as a mixture of the unconjugated form and a number of conjugates. The half-life of uE3 in the maternal blood system is 20 to 30 minutes because the maternal liver quickly conjugates estriol to make it more water soluble for urinary excretion. Estriol levels increase during the course of pregnancy. Decreased uE3 has been shown to be a marker for Down syndrome and trisomy 18. Low levels of estriol also have been associated with overestimation of gestation, pregnancy loss, Smith-Lemli-Opitz, and X-linked ichthyosis (placental sulfatase deficiency). Human Chorionic Gonadotropin (hCG): hCG is a glycoprotein consisting of 2 noncovalently bound subunits. The alpha subunit is identical to the alpha subunits of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH), while the beta subunit has significant homology to the beta subunit of LH and limited similarity to the FSH and TSH beta subunits. The beta subunit determines the unique physiological, biochemical, and immunological properties of hCG. The CGA gene (glycoprotein hormones, alpha polypeptide) is thought to have developed through gene duplication from the LH gene in a limited number of mammalian species. hCG only plays an important physiological role in primates (including humans), where it is synthesized by placental cells, starting very early in pregnancy, and serves to maintain the corpus luteum and, hence, progesterone production, during the first trimester. Thereafter, the concentration of hCG begins to fall as the placenta begins to produce steroid hormones and the role of the corpus luteum in maintaining pregnancy diminishes. Increased total beta hCG levels are associated with Down syndrome, while decreased levels may be
seen in trisomy 18. Elevations of hCG also can be seen in multiple pregnancies, unaffected singleton pregnancies in which the gestational age has been overestimated, triploidy, fetal loss, and hydrops fetales. Inhibin A: Inhibins are a family of heterodimeric glycoproteins that consist of disulfide-linked alpha and beta subunits, primarily secreted by ovarian granulosa cells and testicular Sertoli cells. While the alpha subunits are identical in all inhibins, the beta subunits exist in 2 major forms, termed A and B, each of which can occur in different isoforms. Depending on whether an inhibin heterodimer contains a beta-A or a beta-B chain, they are designated as inhibin A or inhibin B, respectively. Together with the related activins, which are homodimers or heterodimers of beta-A and beta-B chains, the inhibins are involved in gonadal-pituitary feedback and in paracrine regulation of germ cell growth and maturation. During pregnancy, inhibins and activins are produced by the fetoplacental unit in increasing quantities, mirroring fetal growth. Their physiological role during pregnancy is uncertain. They are secreted into the coelomic and amniotic fluid, but only inhibin A is found in appreciable quantities in the maternal circulation during the first and second trimesters. Maternal inhibin A levels are correlated with maternal hCG levels and are abnormal in the same conditions that are associated with abnormal hCG levels (eg, inhibin A levels are typically higher in Down syndrome pregnancies). However, despite their similar behavior, measuring maternal serum inhibin A concentrations in addition to maternal serum hCG concentrations further improves the sensitivity and specificity of maternal multiple marker screening for Down syndrome.

**Useful For:** Prenatal screening for Down syndrome and trisomy 18 Prenatal screening for neural tube defects: (this is only applicable to Part 2 [second trimester] of the test) -Part 2 (second trimester): alpha-fetoprotein

**Interpretation:** Maternal screens provide an estimation of risk, not a diagnosis. A negative result indicates that the estimated risk falls below the screen cutoff. A positive result indicates that the estimated risk exceeds the screen cutoff. Neural Tube Defect (NTD): Screen-negative results indicate that the alpha-fetoprotein (AFP) multiple of the median (MoM) falls below the screen cutoff of 2.50 MoM (5.33 MoM for twins). A negative screen does not guarantee the absence of an NTD. Screen-positive results indicate that the calculated AFP MoM is > or =2.50 MoM (5.33 MoM for twins). Positive results may indicate an increased risk for an open NTD. The actual risk depends on the level of AFP and the individual’s pretest risk of having a child with an NTD based on variables including family history, geographical location, maternal conditions such as diabetes and epilepsy, and use of folate prior to conception. A screen-positive result does not infer a definitive diagnosis of a NTD, but indicates that further evaluation should be considered. Approximately 80% of pregnancies affected with open NTDs have AFP MoM values >2.5. Down Syndrome: Sequential Maternal Screening, Part 2, Serum results are negative when the calculated risk is below 1/270 (0.37%). Negative results mean that the risk is less than the established cutoff; they do not guarantee the absence of Down syndrome. Results are positive when the risk is greater than the established cutoff (> or =1/270 in Sequential Maternal Screening, Part 2, Serum). Positive results are not diagnostic. When both Sequential Maternal Screening Part 1 and Part 2 are performed with a screen cutoff of 1/270, the combination of maternal age, nuchal translucency (NT), pregnancy-associated plasma protein A (PAPP-A), AFP, unconjugated estriol (uE3), human chorionic gonadotropin (hCG), and inhibin A has an overall detection rate of approximately 90% with a false-positive rate of approximately 3% to 4%. In practice, both the detection rate and false-positive rate vary with maternal age. Trisomy 18: In Part 2, the screen cutoff for trisomy 18 is 1 in 100 (1%). Risks that are > or =1% are screen-positive; positive results are not diagnostic. Risks <1% are screen-negative; negative results do not guarantee the absence of trisomy 18. Use caution when revising positive results with earlier dating. Babies with trisomy 18 tend to be small, which can lead to underestimation of gestational age and an increased risk of missing a true-positive. When both Sequential Maternal Screening Part 1 and Part 2 of sequential screening are performed with a screen cutoff of 1/100, the combination of maternal age, PAPP-A, AFP, uE3, and hCG, has an overall detection rate of approximately 90% with a false-positive rate of approximately 0.1%. Follow-up: Verify that all information used in the risk calculation is correct (maternal date of birth, gestational dating, etc). If any information is erroneous, contact the laboratory for a revision. Screen-negative results typically do not warrant further evaluation. If the results are positive, the patient is typically offered counseling, ultrasound, diagnostic testing, and, possibly, a referral to genetics counseling or a high-risk clinic.

**Reference Values:**
An interpretive report will be provided. See Interpretation section for more details.
Serologic Agglut Method 4 Ident (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

Serotonin Receptor Genotype (HTR2A and HTR2C)

Clinical Information: Treatment with specific antidepressant and antipsychotic medications is often guided empirically. Despite the wide array of drugs available for treatment, some patients do not initially respond to treatment and others who respond early may eventually relapse or develop serious side effects. Antidepressant selection may be more effectively guided by genotyping polymorphic genes encoding several cytochrome P450 enzymes, the serotonin transporter, and the serotonin (5-hydroxytryptamine) receptors HTR2A and HTR2C. (1) Drugs that bind to the serotonin receptors have a wide range of effects including altering the activation of the receptors, rendering them more or less sensitive to drug concentration, or blocking the receptor. Variations (polymorphisms) in the genes that encode for the serotonin receptor have been associated with different types of drug responses including: -Allelic variation in the HTR2A gene has been reported to affect response to the selective serotonin reuptake inhibitor (SSRI) citalopram. Alternate antidepressant medications may be considered for patients predicted to respond poorly to citalopram due to polymorphic variants in the HTR2A serotonin receptor. (2) Associations between other antidepressants and response based on HTR2A genotype have been reported, but are less consistent in the literature. -Treatment with antipsychotics results in significant weight gain (2-3 kg/m²) in some patients. Weight gain has been positively correlated with the c.-759C>T polymorphism in the promoter of HTR2C (3) and metabolic syndrome has been associated with c.551-3008C>G. (4) The following table displays the HTR2A/2C variants detected by this assay: Gene Allele cDNA Nucleotide Change HTR2A rs7997012 614-2211T>C HTR2C rs3813929 -759C>T HTR2C rs1414334 551-3008C>G

Useful For: Guiding treatment choice of antidepressant Guiding treatment choice in individuals who have a drug-metabolizer phenotype discordant with CYP450 genotypes Identifying those patients at risk of excessive weight gain or metabolic syndrome when receiving antipsychotic medications

Interpretation: An interpretive report will be provided. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomics Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Reference Values: An interpretive report will be provided.

Serotonin Release Assay (SRA), LMWH

**Reference Values:**

<table>
<thead>
<tr>
<th>LMWH SRA Result</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH Low Dose, 0.1 U/mL</td>
<td>% release</td>
</tr>
<tr>
<td>LMWH Low Dose, 1.0 U/mL</td>
<td>% release</td>
</tr>
<tr>
<td>LMWH High Dose, 50 U/mL</td>
<td>% release</td>
</tr>
</tbody>
</table>

A sample is considered negative if there is: <20% release.

Serotonin Release Assay, Unfractionated Heparin

**Reference Values:**

<table>
<thead>
<tr>
<th>UFH SRA Result</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH Low Dose, 0.1 IU/mL</td>
<td>% release</td>
</tr>
<tr>
<td>UFH Low Dose, 0.5 IU/mL</td>
<td>% release</td>
</tr>
<tr>
<td>UFH High Dose, 100 IU/mL</td>
<td>% release</td>
</tr>
</tbody>
</table>

A sample is considered negative if there is: <20% release.

Serotonin Release Assay, Unfractionated Heparin

**Reference Values:**

| An interpretive comment included with results. |

Serotonin Transporter Genotype, Blood

**Clinical Information:** Serotonin (5-hydroxytryptamine; 5-HT) is a neurotransmitter. The serotonin transporter (5-HTT) modulates neurotransmission by facilitating removal of serotonin from the synapse of serotonergic neurons, resulting in serotonin reuptake into the presynaptic terminus. Other designations for 5-HTT are SLC6A4 (solute carrier family 6 [neurotransmitter transporter, serotonin], member 4), hSERT, OCD1, SERT, sodium-dependent serotonin transporter, and 5-HT transporter. Selective serotonin reuptake inhibitors (SSRIs) block the action of the serotonin transporter and are used to treat depression and other neuropsychiatric disorders. Examples of SSRIs are fluoxetine (Prozac), fluvoxamine (Luvox), escitalopram oxalate (Lexapro), sertraline (Zoloft), citalopram (Celexa), and paroxetine (Paxil, Paxil CR). The 5-HTT gene is located at 17q11.1-q12 and is composed of 14 exons spanning 31 kb. A 44-base pair promoter insertion/deletion polymorphism called LPR, or linked polymorphic region, produces alleles described as long or short. The short allele is dominant and results in decreased concentration of the transporter protein and a poorer response to stressful events. While individuals homozygous for the long allele (l/l) may demonstrate response to SSRI therapy in 3 to 4 weeks, individuals with the short allele (l/s or s/s) may respond more slowly, taking up to 12 weeks.

**Useful For:** Evaluating patients who have failed therapy with selective serotonin reuptake inhibitors (SSRIs) Evaluating patients with treatment-resistant depression Predicting response time to improvement with SSRIs Identifying patients who might respond favorably to a class of antidepressants other than SSRIs. Identifying patients who have diminished amounts of the serotonin transporter and, hence, an altered response to SSRI therapeutics

**Interpretation:** The normal (wildtype) allele yields a long product (l/l). The variant is short/short (s/s). Heterozygotes have a l/s genotype. Individuals homozygous for the long allele (l/l) may respond more rapidly to selective serotonin reuptake inhibitors (SSRI) therapy. Individuals homozygous for the short allele (s/s) may respond more slowly to SSRI therapy and may benefit from a longer trial before...
considering switching to another antidepressant. Even 1 copy of the short allele (heterozygous) decreases the amount of the transporter protein present, increasing the time to response. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomics Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Serotonin Transporter Genotype, Saliva**

**Clinical Information:** Serotonin (5-hydroxytryptamine; 5-HT) is a neurotransmitter. The serotonin transporter (5-HTT) modulates neurotransmission by facilitating removal of serotonin from the synapse of serotonergic neurons, resulting in serotonin reuptake into the presynaptic terminus. Other designations for 5-HTT are SLC6A4 (solute carrier family 6 [neurotransmitter transporter, serotonin], member 4), hSERT, OCD1, SERT, sodium-dependent serotonin transporter, and 5-HT transporter. Selective serotonin reuptake inhibitors (SSRIs) block the action of the serotonin transporter and are used to treat depression and other neuropsychiatric disorders. Examples of SSRIs include fluoxetine (Prozac), fluvoxamine (Luvox), escitalopram oxalate (Lexapro), sertraline (Zoloft), citalopram (Celexa), and paroxetine (Paxil, Paxil CR). The 5-HTT gene is located at 17q11.1-q12 and is composed of 14 exons spanning 31 kb. A 44-base pair promoter insertion/deletion polymorphism called LPR, or linked polymorphic region, produces alleles described as long or short. The short allele is dominant and results in decreased concentration of the transporter protein and a poorer response to stressful events. While individuals homozygous for the long allele (l/l) may demonstrate response to SSRI therapy in 3 to 4 weeks, individuals with the short allele (l/s or s/s) may respond to SSRI therapy more slowly, taking up to 12 weeks.

**Useful For:** Qualifying participants for clinical trials Evaluating patients who have failed therapy with selective serotonin reuptake inhibitors (SSRIs) Evaluating patients with treatment-resistant depression Predicting response time to improvement with SSRIs Identifying patients who might respond favorably to nonselective antidepressants Identifying patients who have diminished amounts of the serotonin transporter and, hence, an altered response to SSRI therapeutics Genotyping patients who prefer not to have venipuncture done

**Interpretation:** The normal (wildtype) allele yields a long product (l/l). The variant is short/short (s/s). Heterozygotes have a l/s genotype. Individuals homozygous for the long allele (l/l) may respond more rapidly to selective serotonin reuptake inhibitor (SSRI) therapy. Individuals homozygous for the short allele (s/s) may respond more slowly to SSRI therapy and may benefit from a longer trial before considering switching to another antidepressant. Even 1 copy of the short allele (heterozygous) decreases the amount of the transporter protein present, increasing the time to response. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomics Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:** 1. Lesch KP, Gutnecht L: Pharmacogenetics of the serotonin transporter. Prog Neuropsychopharmacol Biol Psychiatry 2005;29:1062-1073 2. Genecard at NCBI for 5-HTT. XenneX, Inc. 2005 October 18; Retrieved 1/06; Available at...
Serotonin, 24 Hour, Urine

**Clinical Information:** Serotonin (5-hydroxytryptamine) is synthesized from the essential amino acid tryptophan via the intermediate 5-hydroxytryptophan (5-HP, 5-HTP). Serotonin production sites are the central nervous system (CNS), where it acts as a neurotransmitter, and neuroectodermal cells, chiefly gastrointestinal (GI) enterochromaffin cells (EC-cells). The CNS and peripheral serotonin pools are isolated from each other. EC-cell production accounts for 80% of the body’s serotonin content. Many different stimuli can release serotonin from EC-cells. Once secreted, in concert with other gut hormones, serotonin increases GI blood flow, motility, and fluid secretion. On first pass through the liver 30% to 80% of serotonin is metabolized, predominately to 5-hydroxyindoleacetic acid (5-HIAA), which is excreted by the kidneys. Ninety percent of the remainder is metabolized in the lungs, also to 5-HIAA. Of the remaining 10%, almost all is taken up by platelets, where it remains until it is released during clotting, promoting further platelet aggregation. The main diseases that may be associated with measurable increases in serotonin are neuroectodermal tumors, in particular tumors arising from EC-cells, which are termed carcinoids. They are subdivided into foregut carcinoids, arising from respiratory tract, stomach, pancreas, or duodenum (approximately 15% of cases); midgut carcinoids, occurring within jejunum, ileum, or appendix (approximately 70% of cases); and hindgut carcinoids, which are found in the colon or rectum (approximately 15% of cases). The enzyme 5-HTP decarboxylase, which converts the intermediate 5-HTP to serotonin, is present in midgut tumors, but is absent or present in low concentrations in foregut and hindgut tumors. Carcinoids display a spectrum of aggressiveness with no clear distinguishing line between benign and malignant. The majority of carcinoid tumors do not cause significant clinical disease. Those tumors that behave more aggressively tend to cause nonspecific GI disturbances, such as intermittent pain and bloating, for many years before more overt symptoms develop.

In advanced tumors, morbidity and mortality relate as much, or more, to the biogenic amines, chiefly serotonin, and peptide hormones secreted, as to local and distant spread. The symptoms of this so-called carcinoid syndrome consist of flushing, diarrhea, right-sided valvular heart lesions, and bronchoconstriction. All of these symptoms are at least partly caused by serotonin. The carcinoid syndrome is usually caused by midgut tumors, as foregut and hindgut neoplasms produce far lesser amounts of serotonin. Because midgut tumors drain into the portal circulation, which passes into the liver, undergoing extensive hepatic (first-pass) serotonin degradation, symptoms do not usually occur until liver or other distant metastases have developed, producing serotonin that bypasses the hepatic degradation. Serotonin production by disseminated carcinoid tumors can sometimes be so substantial that body tryptophan stores become depleted and clinical tryptophan deficiency, resembling pellagra (trial of diarrhea, dementia, and dermatitis), develops. Diagnosis of carcinoid tumors with symptoms suggestive of carcinoid syndrome rests on measurements of circulating and urine serotonin, urine 5-HIAA (HIAA / 5-Hydroxyindoleacetic Acid [5-HIAA], 24 Hour, Urine), and serum chromogranin A (CGAK / Chromogranin A, Serum), a peptide that is cosecreted alongside specific hormones by neuroectodermal cells. Urine serotonin is, in most circumstances, the least likely marker to be elevated (see Interpretation).

**Useful For:** The diagnosis of a small subgroup of carcinoid tumors that produce predominately 5-hydroxytryptophan (5-HP, 5-HTP), but very little serotonin and chromogranin A. Follow-up of patients with known or treated carcinoid tumors that produce predominately 5-HP, but very little serotonin and chromogranin A.

**Interpretation:** It is usually impossible to diagnose asymptomatic, small carcinoid tumors by measurement of serum or urine serotonin, urine 5 hydroxyindoleacetic acid (5-HIAA), or serum chromogranin A. By contrast, 1 or more of these markers are elevated in most patients with more advanced and symptomatic tumors, usually to levels several times the upper limit of the reference interval. In patients with advanced and symptomatic tumors the following patterns of tumor marker elevations are observed: 1. Serum or whole blood serotonin is elevated in nearly all patients with midgut tumors, but only in approximately 50% of those with foregut carcinoids, and in no more than 20% of individuals with hindgut tumors, because foregut and hindgut tumors often have low or absent 5-hydroxytryptophan (5-HTP) decarboxylase activity and, therefore, may produce little, if any, serotonin. 2. Urine 5-HIAA is elevated in almost all carcinoid-syndrome patients with midgut tumors, in about 30% of individuals with foregut carcinoids, but almost never in hindgut tumors. 3. Serum chromogranin A measurements are...
particularly suited for diagnosing hindgut tumors, being elevated in nearly all cases, even though serotonin and 5-HIAA are often normal. Chromogranin A is also elevated in 80% to 90% of patients with symptomatic foregut and midgut tumors. Urine serotonin is in most circumstances the least likely marker to be elevated. The exception is tumors (usually foregut tumors) that produce predominately 5-HTP, rather than serotonin, and also secrete little, if any, chromogranin A. In this case, circulating chromogranin A, circulating serotonin levels, and urine 5-HIAA levels would not be elevated. However, the kidneys can convert 5-HTP to serotonin, leading to high urine serotonin levels. Urine serotonin measurements are not commonly employed in carcinoid tumor follow-up. The exceptions are patients with tumors that almost exclusively secrete 5-HTP, as summarized above. In these individuals, urine serotonin is the tumor marker of choice to monitor disease progression. In all other patients, disease progression is monitored best using urinary 5-HIAA and serum chromogranin A measurements. These markers are usually proportional to the patient’s tumor burden over a wide range of tumor extent and tumor secretory activity.

**Reference Values:**
< or =210 mcg/24 hours
Reference values apply to all ages.

**Clinical References:**

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**Serotonin, Blood**

**Clinical Information:** Serotonin (5-hydroxytryptamine: 5-HT) is synthesized from the essential amino acid tryptophan via the intermediate 5-hydroxytryptophan (5-HTTP). 5-HT production sites are the central nervous system (CNS), where it acts as a neurotransmitter, and neuroectodermal cells, chiefly gastrointestinal (GI) enterochromaffin cells (EC-cells). The CNS and peripheral 5-HT pools are isolated from each other. EC-cell production accounts for 80% of the body’s 5-HT content. Many different stimuli can release 5-HT from EC-cells. Once secreted, in concert with other gut hormones, 5-HT increases GI blood flow, motility, and fluid secretion. On first pass through the liver, 30% to 80% of 5-HT is metabolized, predominately to 5-hydroxyindoleacetic acid (5-HIAA), which is excreted by the kidneys. Ninety-percent of the remainder is metabolized in the lungs, also to 5-HIAA. Of the remaining 10%, almost all is taken up by platelets, where it remains until it is released during clotting, promoting further platelet aggregation. The main diseases that may be associated with measurable increases in 5-HT are neuroectodermal tumors, in particular, tumors arising from EC-cells, which are termed carcinoids. They are subdivided into foregut carcinoids, arising from respiratory tract, stomach, pancreas, or duodenum (approximately 15% of cases); midgut carcinoids, occurring within jejunum, ileum, or appendix (approximately 70% of cases); and hindgut carcinoids, which are found in the colon or rectum (approximately 15% of cases). Carcinoids display a spectrum of aggressiveness with no clear distinguishing line between benign and malignant. The majority of carcinoid tumors do not cause significant clinical disease. Those tumors that behave more aggressively tend to cause nonspecific GI disturbances, such as intermittent pain and bloating, for many years before more overt symptoms develop. In advanced tumors, morbidity and mortality relate as much, or more, to the biogenic amines, chiefly 5-HT, and peptide hormones secreted, as to local and distant spread. The symptoms of this so-called carcinoid syndrome consist of flushing, diarrhea, right-sided valvular heart lesions, and bronchoconstriction. All of these symptoms are at least partly caused by 5-HT. The carcinoid syndrome is usually caused by midgut tumors, as foregut and hindgut neoplasms produce far lesser amounts of 5-HT. Since midgut tumors drain into the portal circulation, which passes into the liver, symptoms do not usually occur until liver or other distant metastases have developed, bypassing the extensive hepatic first-pass 5-HT degradation. Serotonin production by disseminated carcinoid tumors can sometimes be
so substantial that body tryptophan stores become depleted and clinical tryptophan deficiency, resembling pellagra (triad of diarrhea, dementia, and dermatitis), develops. Diagnosis of carcinoid tumors with symptoms suggestive of carcinoid syndrome rests on measurements of circulating and urinary 5-HT, urinary 5-HIAA (HIAA / 5-Hydroxyindoleacetic Acid [5-HIAA], 24 Hour, Urine), and serum chromogranin A (CGAK / Chromogranin A, Serum), a peptide that is cosecreted alongside specific hormones by neuroectodermal cells.

**Useful For:** In conjunction with, or as an alternative to first-order test in the differential diagnosis of isolated symptoms suggestive of carcinoid syndrome, in particular flushing (5-HIAA or serum chromogranin A measurements are first-line tests) Second-order test in the follow-up of patients with known or treated carcinoid tumors in whole blood specimens

**Interpretation:** Metastasizing midgut carcinoid tumors usually produce blood or serum 5-hydroxytryptamine (5-HT) concentrations greater than 1,000 ng/mL. However, elevations above 400 ng/mL are suggestive of carcinoid tumors as the cause of carcinoid syndrome-like symptoms. Lesser increases may be nonspecific or drug-related (see Cautions). Only a minority of patients with carcinoid tumors will have elevated 5-HT levels. It is usually impossible to diagnose small carcinoid tumors (>95% of cases) without any symptoms suggestive of carcinoid syndrome by measurement of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), or chromogranin A. In patients with more advanced tumors, circulating 5-HT is elevated in nearly all patients with midgut tumors, but only in approximately 50% of those with foregut carcinoids, and in no more than 20% of individuals with hindgut tumors. Foregut and hindgut tumors often have low or absent 5-hydroxytryptophan (5-HTP) decarboxylase activity and, therefore, may produce little if any 5-HT. Urinary 5-HIAA is elevated in almost all carcinoid-syndrome patients with midgut tumors, in about 30% of individuals with foregut carcinoids, but almost never in hindgut tumors. Serum chromogranin A measurements are particularly suited for diagnosing hindgut tumors, being elevated in nearly all cases, even though 5-HT and 5-HIAA are often normal. Chromogranin A is also elevated in 80% to 90% of patients with foregut and midgut tumors. Therefore, to achieve maximum sensitivity in the initial diagnosis of suspected carcinoid tumors, 5-HT in serum/blood, 5-HIAA in urine, and serum chromogranin A should all be measured. In most cases, if none of these 3 analytes is elevated, carcinoids can be excluded as a cause of symptoms suggestive of carcinoid syndrome. For some cases, additional tests, such as urinary 5-HT measurement will be required. An example would be a nonchromogranin-secreting foregut tumor that only produces 5-HTP, rather than 5-HT. In this case, circulating chromogranin, 5-HT levels, and urinary 5-HIAA levels would not be elevated. However, the kidneys can convert 5-HTP to 5-HT, leading to high urinary 5-HT levels. Disease progression can be monitored in patients with serotonin-producing carcinoid tumors by measurement of 5-HT in blood. However, at levels above approximately 5,000 ng/mL, the serotonin storage capacity of platelets becomes limiting, and there is no longer a linear relationship between tumor burden and blood 5-HT levels. Urinary 5-HIAA and serum chromogranin A continue to increase in proportion to the tumor burden to much higher 5-HT production levels, and are therefore better suited for follow-up in patients with extensive disease.

**Reference Values:**

< or =330 ng/mL

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.

amino acid tryptophan via the intermediate 5-hydroxytryptophan (5-HP). 5-HT production sites are the central nervous system (CNS), where it acts as a neurotransmitter, and neuroectodermal cells, chiefly gastrointestinal (GI) enterochromaffin cells (EC-cells). The CNS and peripheral 5-HT pools are isolated from each other. EC-cell production accounts for 80% of the body's 5-HT content. Many different stimuli can release 5-HT from EC-cells. Once secreted, in concert with other gut hormones, 5-HT increases GI blood flow, motility, and fluid secretion. On first pass through the liver 30% to 80% of 5-HT is metabolized, predominately to 5-hydroxyindoleacetic acid (5-HIAA), which is excreted by the kidneys. Ninety-percent of the remainder is metabolized in the lungs, also to 5-HIAA. Of the remaining 10%, almost all is taken up by platelets, where it remains until it is released during clotting, promoting further platelet aggregation. The main diseases that may be associated with measurable increases in 5-HT are neuroectodermal tumors, in particular tumors arising from EC-cells, which are termed carcinoids. They are subdivided into foregut carcinoids, arising from respiratory tract, stomach, pancreas, or duodenum (approximately 15% of cases); midgut carcinoids, occurring within jejunum, ileum, or appendix (approximately 70% of cases); and hindgut carcinoids, which are found in the colon or rectum (approximately 15% of cases). Carcinoids display a spectrum of aggressiveness with no clear distinguishing line between benign and malignant. The majority of carcinoid tumors do not cause significant clinical disease. Those tumors that behave more aggressively tend to cause nonspecific GI disturbances, such as intermittent pain and bloating, for many years before more overt symptoms develop. In advanced tumors, morbidity and mortality relate as much, or more, to the biogenic amines, chiefly 5-HT, and peptide hormones secreted, as to local and distant spread. The symptoms of this so-called carcinoid syndrome consist of flushing, diarrhea, right-sided valvular heart lesions, and bronchoconstriction. All of these symptoms are at least partly caused by 5-HT. The carcinoid syndrome is usually caused by midgut tumors, as foregut and hindgut neoplasms produce far less 5-HT. Since midgut tumors drain into the portal circulation, which passes into the liver, symptoms do not usually occur until liver or other distant metastases have developed, bypassing the extensive hepatic first-pass 5-HT degradation. Serotonin production by disseminated carcinoid tumors can sometimes be so substantial that body tryptophan stores become depleted and clinical tryptophan deficiency, resembling pellagra (triad of diarrhea, dementia, and dermatitis), develops. Diagnosis of carcinoid tumors with symptoms suggestive of carcinoid syndrome rests on measurements of circulating and urinary 5-HT, urinary 5-HIAA (HIAA / 5-Hydroxyindoleacetic Acid [5-HIAA], 24 Hour, Urine), and serum chromogranin A (CGAK / Chromogranin A, Serum), a peptide that is cosecreted alongside specific hormones by neuroectodermal cells.

**Useful For:** In conjunction with, or as an alternative to first-order test in the differential diagnosis of isolated symptoms suggestive of carcinoid syndrome, in particular flushing (5-HIAA or serum chromogranin A measurements are first-line tests) Second-order test in the follow-up of patients with known or treated carcinoid tumors in serum specimens

**Interpretation:** Metastasizing midgut carcinoid tumors usually produce blood or serum 5-hydroxytryptamine (5-HT) concentrations greater than 1,000 ng/mL. However, elevations above 400 ng/mL are suggestive of carcinoid tumors as the cause of carcinoid syndrome-like symptoms. Lesser increases may be nonspecific or drug-related (see Cautions). Only a minority of patients with carcinoid tumors will have elevated 5-HT levels. It is usually impossible to diagnose small carcinoid tumors (>95% of cases) without any symptoms suggestive of carcinoid syndrome by measurement of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), or chromogranin A. In patients with more advanced tumors, circulating 5-HT is elevated in nearly all patients with midgut tumors, but only in approximately 50% of those with foregut carcinoids, and in no more than 20% of individuals with hindgut tumors. Foregut and hindgut tumors often have low or absent 5-hydroxytryptophan (5-HTP) decarboxylase activity and, therefore, may produce little if any 5-HT. Urinary 5-HIAA is elevated in almost all carcinoid-syndrome patients with midgut tumors, in about 30% of individuals with foregut carcinoids, but almost never in hindgut tumors. Serum chromogranin A measurements are particularly suited for diagnosing hindgut tumors, being elevated in nearly all cases, even though 5-HT and 5-HIAA are often normal. Chromogranin A is also elevated in 80% to 90% of patients with foregut and midgut tumors. Therefore, to achieve maximum sensitivity in the initial diagnosis of suspected carcinoid tumors, 5-HT in serum/blood, 5-HIAA in urine, and serum chromogranin A should all be measured. In most cases, if none of these 3 analytes is elevated, carcinoids can be excluded as a cause of symptoms suggestive of carcinoid syndrome. For some cases, additional tests, such as urinary 5-HT measurement will be required. An example would be a nonchromogranin-secreting foregut tumor that only produces 5-HP.
rather than 5-HT. In this case, circulating chromogranin, 5-HT levels, and urinary 5-HIAA levels would not be elevated. However, the kidneys can convert 5-HP to 5-HT, leading to high urinary 5-HT levels. Disease progression can be monitored in patients with serotonin-producing carcinoid tumors by measurement of 5-HT in blood. However, at levels above approximately 5,000 ng/mL, the serotonin storage capacity of platelets becomes limiting, and there is no longer a linear relationship between tumor burden and blood 5-HT levels. Urinary 5-HIAA and serum chromogranin A continue to increase in proportion to the tumor burden to much higher 5-HT production levels, and are therefore better suited for follow-up in patients with extensive disease.

Reference Values:
< or =230 ng/mL


SERPZ
SERPINA1 Gene, Full Gene Analysis

Clinical Information: Alpha-1-antitrypsin (A1A) is a protein that inhibits the enzyme neutrophil elastase. It is predominantly synthesized in the liver and secreted into the bloodstream. The inhibition function is especially important in the lungs because it protects against excess tissue degradation. Tissue degradation due to A1A deficiency is associated with an increased risk for early onset panlobular emphysema, which initially affects the lung bases (as opposed to smoking-related emphysema, which presents with upper lung field emphysema). Patients may become symptomatic in their 30s and 40s. The most frequent symptoms reported in a National Institute of Health study of 1,129 patients with severe deficiency (mean age 46 years) included cough (42%), wheezing (65%), and dyspnea with exertion (84%). Many patients were misdiagnosed as having asthma. It is estimated that approximately one-sixth of all lung transplants are for A1A deficiency. Liver disease can also occur, particularly in children; it occurs much less commonly than emphysema in adults. A1A deficiency is a relatively common disorder in Northern European Caucasians. The diagnosis of A1A deficiency is initially made by quantitation of protein levels in serum followed by phenotyping-determination of specific allelic variants by isoelectric focusing (IEF), genotyping-DNA based detection of specific mutations, or proteotyping-using liquid chromatography-tandem mass spectrometry (LC-MS/MS). While there are many different alleles in this gene, only 3 are common. The 3 major alleles include: M (full functioning, normal allele), S (associated with reduced levels of protein), and Z (disease-causing mutation associated with liver disease and premature emphysema). The S and Z alleles account for the majority of the abnormal alleles detected in affected patients. As a codominant disorder, both alleles are expressed. An individual of SZ or S- null genotype may have a small increased risk for emphysema (but not liver disease) due to slightly reduced protein levels. On the other hand, an individual with the ZZ genotype is at greater risk for early onset liver disease and premature emphysema. Smoking appears to hasten development of emphysema by 10 to 15 years. These individuals should be monitored closely for lung and liver function. Historically, IEF phenotyping has been the primary method for characterizing variants, though in some cases the interpretation is difficult and prone to error. Serum quantitation is helpful in establishing a diagnosis but can be influenced by other factors. IEF phenotyping, LC-MS/MS proteotyping, and DNA-based genotyping are routinely used to test for deficiency alleles, but can miss disease alleles other than the S and Z alleles. In patients suspected to have alpha-1 antitrypsin deficiency based on clinical findings or serum alpha-1-antitrypsin (AAT) levels, who do not have evidence of the SZ or ZZ genotype by routine methods, this gene analysis assay may provide useful information. Full sequencing of the SERPINA1 coding region is performed for the detection of rare non-S or non-Z disease mutations. See Alpha-1-Antitrypsin-A Comprehensive Testing Algorithm in Special Instructions.

Useful For: Identification of causative mutations when a deficient serum level of alpha-1-antitrypsin is not explained by routine testing, such as proteotyping, genotyping, or isoelectric focusing phenotyping.
Determining the specific allelic variant (full gene analysis) for prognosis and genetic counseling

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FSERT**

**Sertraline (Zoloft) and Desmethylsertraline**

**Reference Values:**
Sertraline:
- Reference Range: 30 - 200 ng/mL
- Report Limit 10 ng/mL

Desmethylsertraline: ng/mL
- No reference range provided

The stated reference range is the range of observed steady-state concentrations in individuals receiving therapeutic dosage regimens of sertraline. This is not a defined therapeutic range.
- Report Limit 10 ng/mL

**FSESG**

**Sesame Seed IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
< 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**SESA**

**Sesame Seed, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**SCDGP 62190**

**Severe Combined Immunodeficiency (SCID) Gene Panel**

**Clinical Information:** Severe combined immunodeficiency (SCID) is characterized by the absence of, or dysfunction of T lymphocytes, which affects both cellular and humoral adaptive immunity, resulting in a severe form of inherited primary immunodeficiency that may be life-threatening. In classic form, SCID presents in infancy with persistent respiratory and gastrointestinal infections, failure to thrive, or graft-versus-host disease (due to engraftment of maternal T cells). The absence of lymphoid tissue, immunoglobulins, and T lymphocytes may also be noted. Typically, patients will have less than 300 autologous CD3 T cells/mL blood and will require immediate medical intervention. Atypical or "leaky" SCID tends to present later (ie, over 12 months of age) with recurrent, severe, and prolonged viral infections, bronchiectasis, autoimmune manifestations including cytopenias, and failure to thrive. Patients may display partial or restricted antigen-specific antibody responses. Leaky SCID is also related to hypomorphic variants in genes normally associated with classic SCID, as indicated above. Omenn syndrome, a form of leaky SCID that typically presents in infancy, is characterized by erythroderma, alopecia, hepatosplenomegaly, and lymphadenopathy. Laboratory findings may include elevated IgE, eosinophilia, and lymphocytosis. Omenn syndrome is due to genetic variants in at least 7 different genes that allow for partial activity, although disease severity is likely only partially attributable to genotype. While RAG1 and RAG2 hypomorphic variants are most often associated with leaky SCID or Omenn syndrome, patients may have variants affecting other genes/proteins, such as Artemis or Interleukin-7 receptor (IL-7R) alpha. There may be forms of leaky SCID with hypomorphic variants in these genes that...
do not have the associated Omenn syndrome phenotype. SCID can be classified as T-B+ or T-B- SCID, with further subdivision possible based on the presence or absence of NK cells. T-B+ SCID, characterized by impaired development of mature T-cells along with present but non-functional B-cells, is most often caused by genetic variants that affect cytokine-mediated signaling. X-linked SCID is due to mutations in the IL2RG gene, which encodes the common gamma chain that is a part of the IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 receptors. Autosomal recessive forms due to variants in JAK3 or IL7R also disrupt cytokine signaling. Genetic variants in one of the four CD3 genes (CD3G, CD3D, CD3E, and CD247(CD3Z)) inhibit CD3 signaling and also cause T-B+ SCID. T-B+ SCID may also be due to coroinin-1A deficiency causing disruption of thymic egress of T cells and defective T cell locomotion, or due to CD45 deficiency (caused by variants in PTPRC). Patients with coroinin-1A deficiency may also have other syndromic manifestations. T-B-SCID is typically characterized by a defect in V(D)J recombination. V(D)J recombination begins with proteins encoded by RAG1 and RAG2 forming a heterodimer and making a single-stranded nick and forming hairpin structured ends between a coding element (V, D, or J segment) and the recombination signal sequence. Then, in the processing phase, the DNA-protein kinase complex (including a protein encoded by PRKDC) binds to and opens the hairpin structure by phosphorylating Artemis (encoded by DCLRE1C). Prior to ligation of the open ends by LIG4/XRC4 and Cernunnos/XLF (encoded by NHEJ1), additional editing takes place. Adenosine deaminase (ADA) deficiency, which results in accumulation of metabolic by-products that are toxic to lymphocytes, and results in T-B- and NK-SCID. It accounts for approximately 15% of cases and is inherited as an autosomal recessive condition, which may include neurological problems (ie, cognitive impairment, hearing/visual impairment, and movement disorders) in addition to SCID. Reticular dysgenesis, due to genetic variants in AK2, is the most severe form of combined immunodeficiency and is characterized by congenital agranulocytosis, lymphopenia, lymphoid and thymic hypoplasia, along with bilateral sensorineural deafness. Subsets of T cells may be decreased due to genetic variants in certain genes, without an appreciable effect on other T cell subsets. For example, genetic variants in CD8A, ZAP70, TAP1, TAP2, or TAPBP can result in absent or reduced CD8+ T cells in the presence of normal quantity of CD4+ T cells. In contrast, genetic variants in CIITA, RFXANK, RFX5, or RFXAP result in absent or reduced CD4+ T cells. These genes are associated with Bare Lymphocyte Syndromes types 1 and 2 respectively, or MHC class I and II deficiencies. In addition, variants in ITK, MAGT1, RHOH, STK4, TRAC, LCK, MAL1, IL21, IL21R, TNFRSF4 (OX40), IKBKB, CD27, or CTPS1 are thought to generally result in combined immunodeficiency that is generally less clinically profound than severe combined immunodeficiency. Several combined immunodeficiencies are associated other features and syndromes. Variants in WAS and WIPF1 present with combined immunodeficiency and congenital thrombocytopenia, while variants in RBM8A are associated with thrombocytopenia-absent radius (TAR) syndrome. DNA repair defects are commonly observed along with combined immunodeficiency in Ataxia-telangiectasia (due to variants in ATM). Thymic defects with additional congenital anomalies may be observed in DiGeorge syndrome (represented on this panel by TBX1), CHARGE syndrome (due to variants in CHD7 or SEMA3E), and patients with genetic variants in FOXN1. Immune-osseous dysplasias along with combined immunodeficiency may be observed in cartilage hair hypoplasia (due to variants in RMRP), while those with variants in STAT5B may have growth hormone insensitivity. Combined immunodeficiency (CID) along with defects of vitamin B12 and folate metabolism may be observed in patients with genetic variants in SLC46A1 or MTHFD1. Anhidrotic ectodermal dysplasia with immunodeficiency results from genetic variants in IKBKG (NEMO) or NFKBIA (IKBA). Calcium channel defects are an associated feature in those with variants in ORAI1 or STIM1. In addition to CID, patients with variants in TTC7A may have multiple intestinal atresias. Barth syndrome along with combined immunodeficiency can be observed in patients with variants in TAZ. Some of these defects can be identified by newborn screening (NBS) for SCID, while others do not present with severe enough T cell lymphopenia in the neonatal period to be identified by NBS. Table 1. Genes included in the Severe Combined Immunodeficiency (SCID)/Combined Immunodeficiency (CID)/T-cell Lymphopenia/Deficiency/Bare Lymphocyte Syndrome (BLS)/EBV-associated Primary Immunodeficiency Gene Panel GENE SYMBOL (ALIAS) PROTEIN OMIM INCIDENCE INHERITANCE PHENOTYPE DISORDER ADA (ADA1) Adenosine deaminase 608958 1-9 per million live births AR, partial ADA deficiency may lead to delayed or milder presentation SCID (T-B-, Ig-, NK-) ADA2 (CECR1) Adenosine deaminase CECR1 isoform a precursor 607575 AR SCID (T-, B-/normal, Ig- with granulocytopenia, deafness), reticular dysgenesis ATM Serine-protein kinase ATM 607585 1/40,000-100,000 AR Ataxia-telangiectasia and
combined immunodeficiency (T with abnormal proliferation to mitogens, B+, Ig often decreased [particularly IgA, IgE, and IgG with increased IgM monomers]) CD247 (CD3Z) T-cell surface glycoprotein CD3 zeta chain isoform 1 precursor 186780 AR SCID (T- B-(normal), Ig- NK normal, no gamma/delta T cells CD27 CD277 antigen precursor 186771 AR Combined immunodeficiency (T+ B no memory, Ig hypogammaglobulinemia following EBV), lymphoproliferative syndrome 2 CD3D T-cell surface glycoprotein CD3 delta chain isoform A precursor 186790 AR SCID (T+B+, Ig-, NK+, no gamma/delta T cells) CD3E T-cell surface glycoprotein CD3 epsilon chain precursor 186830 AR SCID (T-B+, Ig-, NK+, no gamma/delta T cells) CD3G T-cell surface glycoprotein CD3 gamma chain precursor 186740 AR Combined immunodeficiency (T (normal with reduced TCR expression, B+ Ig+) CD8A T-cell surface glycoprotein CD8 alpha chain isoform 1 precursor 186910 AR CD8 deficiency (normal CD4 cells, B+, Ig+) CHD7 Chromodomain-helicase-DNA-binding protein 7 isoform 1 608892 AD Combined immunodeficiency (T decreased/normal [response to PHA may be decreased], B+, Ig decreased/normal), CHARGE syndrome CIITA MHC class II transactivator isoform 2 600005 AR Combined immunodeficiency (decreased CD4 cells and absent MHC II expression on lymphocytes, B+, Ig decreased/normal) CORO1A Coronin-1A 605000 AR SCID (T+B+, Ig-, with detectable thymus EBV-associated B-cell lymphoproliferation), CGD CTTPS1 CTP synthase 1 isoform 1 a 123860 AR Combined immunodeficiency (T decreased/normal with decreased/normal proliferation, B decreased/normal, Ig high/normal) DCLRE1C (ARTEMIS) Protein Artemis isoform a 605988 1/2,000 in Athabaskan-speaking populations AR SCID (T-B-, Ig- with radiation sensitivity), ommen syndrome, FOXL1 Forkhead box protein N1 600838 AR Combined immunodeficiency (T markedly decreased, B+, Ig decreased) congenital alopecia, and nail dystrophy, nude SCID GATA2 Endothelial transcription factor GATA-2 isoform 1 137395 AD Immunodeficiency with multineuigene cytopenias, emberger syndrome, susceptibility to acute myeloid Leukemia and myelodysplastic syndrome IKKB Inhibitor of nuclear factor kappa-B kinase subunit beta isoform 1 603258 Rare AR Combined immunodeficiency (T normal total with absent regulatory and gamma-delta, B normal [impaired BCR activation], Ig decreased) IKBKG (NEMO) NF-kappa-B essential modulator isoform a 300248 Rare XL Combined immunodeficiency (T decreased/normal with poor activation, B normal [low memory B cells], Ig decreased with poor specific antibody responses), anhidrotic ectodermal dysplasia, mycobacterial susceptibility IL21 Interleukin-21 isoform 1 precursor 605384 AR Combined immunodeficiency (T normal number but low function, B low, IgG deficiency), severe early onset colitis IL21R Interleukin-21 receptor isoform 1 precursor 1 605383 AR/AD Combined immunodeficiency (abnormal T cell cytokine production and abnormal proliferation to specific stimuli, B normal, Ig normal but impaired specific responses), elevated IgE (autosomal dominant) IL2RG Cytokine receptor common subunit gamma subunit precursor 308380 Approximately 1/50,000-100,000 live births XL SCID (T-, B+(normal to increased), Ig-, NK-) IL7R Interleukin-7 receptor subunit alpha precursor 146661 AR SCID (T- B+, Ig decreased, NK+), ommen syndrome ITK Tyrosine-protein kinase ITK/TSK 186973 Rare AR Immunodeficiency (progressive T cell disease with normal B cells and normal/decreased Ig), lymphoproliferative syndrome 1, EBV susceptibility JAK3 Tyrosine-protein-kinase JAK3 600173 Rare AR Combined immunodeficiency (T decreased/normal [response to PHA may be decreased], B+, Ig normal [impaired BCR activation], Ig decreased/normal), severe early onset colitis IL21R Interleukin-21 receptor isoform 1 precursor 1 605383 AR/AD Combined immunodeficiency (T normal total numbers but Cd4 lymphopenia, low Treg, restricted T repertoire and impaired TCR signaling; B normal, Ig: normal IgG and IgA with increased IgM) LIG4 DNA ligase 4 601837 AR SCID (T-B-, NK+ with radiation sensitivity, microcephaly, and developmental defects), ommen syndrome, Dubowitz syndrome MAGT1 Magnesium transporter protein 1 300715 Approximately 1/50,000-100,000 live births XL SCID (T-, B+(normal to increased), Ig-, NK-) IL7R Interleukin-7 receptor subunit alpha precursor 146661 AR SCID (T- B+, Ig decreased, NK+), ommen syndrome ITK Tyrosine-protein-kinase ITK/TSK 186973 Rare AR Immunodeficiency (progressive T cell disease with normal B cells and normal/decreased Ig), lymphoproliferative syndrome 1, EBV susceptibility JAK3 Tyrosine-protein-kinase JAK3 600173 Rare AR Combined immunodeficiency (T decreased/normal with decreased/normal proliferation, B decreased/normal, Ig decreased/normal) MALT1 Mucosa-associated lymphoid tissue lymphoma translocation protein 1 isoform 1 186910 AR Combined immunodeficiency (T decreased CD4 and impaired proliferation in response to CD3, B+ Ig+), EBV susceptibility susceptibility MALT1 Mucosa-associated lymphoid tissue lymphoma translocation protein 1 isoform 1 604860 AR Immunodeficiency (T normal with impaired proliferation; B+, Ig normal with impaired antibody response) MTHFD1 C-1-tetrahydrofolate synthase, cytoplasmic 172460 AR Combined immunodeficiency (T normal with absent regulatory and gamma-delta, B normal [impaired BCR activation], Ig decreased/normal), severe early onset colitis
Neutrophil immunodeficiency syndrome; identified with T cell lymphopenia in NBS SCID; may affect T cell numbers and/or function RAG1 V(D)J recombination-activating protein 1 179615 Approximately 1/100,000 live births AR SCID (T-B-, Ig-, NK+), omenn syndrome RAG2 V(D)J recombination-activating protein 2 179616 Approximately 1/100,000 live births AR SCID (T-B-, Ig-, NK+), omenn syndrome RBM8A RNA-binding protein 8A 605313 AR Thrombocytopenia-absent radius syndrome RFX5 DNA-binding protein RFX5 601863 AR Bare lymphocyte syndrome (decreased CD4 cells and absent MHC II expression on lymphocytes, B+, Ig+ (decreased)) RFXANK DNA-binding protein RFXANK isoform A 603200 AR Bare lymphocyte syndrome (decreased CD4 cells and absent MHC II expression on lymphocytes, B+, Ig+ (decreased)) RFXAP Regulatory factor X-associated protein 601861 AR Bare lymphocyte syndrome (decreased CD4 cells and absent MHC II expression on lymphocytes, B+, Ig+ (decreased)) RHOD Rho-related GTP-binding protein Rhod precursor 602037 AR Combined immunodeficiency (T normal but low naive T cells, restricted repertoire, and impaired proliferation in response to CD3; B+, Ig+) RMRP RNA component of mitochondrial RNA processing endoribonuclease 157660 AR Cartilage-hair hypoplasia, SCID (T severely decreased to normal with impaired proliferation; B-, Ig normal or reduced); Omenn syndrome SEMA3E Semaphorin-3E isoform 1 precursor 608166 AD CHARGE syndrome; Combined immunodeficiency (T decreased normal [response to PHA may be decreased], B+, Ig decreased (normal); SH2D1A SH2 domain-containing protein 1A isoform 1 300490 1/million males XL X-linked lymphoproliferative syndrome (normal/increased activated T cells, reduced memory B cells, partially defective NK cell and CTL cytotoxic activity) SLC46A1 Proton-coupled folate transporter isoform 1 611672 AR Combined immunodeficiency related to folate deficiency (T variable, B variable, Ig decreased); megaloblastic anemia STAT5B Signal transducer and activator of transcription 5B 604260 Rare AR Immunodeficiency (T modestly decreased, B+, Ig+) with growth hormone insensitivity STIM1 Stromal interaction molecule 1 isoform 2 precursor 605921 AR/AD Immunodeficiency (T normal with defective TCR mediated activation, B+, Ig+) (AR), STK4 SERINE/THREONINE PROTEIN KINASE 4 614868 AR Combined immunodeficiency (T: altered proportion of terminal differentiated effector memory cells with restricted repertoire, low naive T cells, impaired proliferation; B decreased, Ig high) TAP1 Antigen peptide transporter 1 isoform 1 170260 AR Bare lymphocyte syndrome (decreased CD8 with absent MHC I expression on lymphocytes, normal B cells, normal Ig) with vasculitis TAP2 Antigen peptide transporter 2 isoform 2 170261 AR Bare lymphocyte syndrome (decreased CD8 with absent MHC I expression on lymphocytes, normal B cells, normal Ig) with vasculitis TAPBP Tapasin isoform 1 precursor 601962 AR Bare lymphocyte syndrome (decreased CD8 with absent MHC I expression on lymphocytes, normal B cells, normal Ig) with vasculitis TAZ Tafazzin isoform 1 300394 XL Barth syndrome TBX1 T-box transcription factor TBX1 isoform C 602054 AD DiGeorge syndrome with immunodeficiency (T decreased or normal, B normal, Ig normal or decreased) TNFRSF4 (OX40) Tumor necrosis factor receptor superfamily member 4 precursor 600315 AR Immunodeficiency (normal T cell numbers with decreased antigen specific memory CD4; normal B cell numbers with reduced memory B cells; normal Ig) TRAC T cell receptor alpha constant 186880 AR Immunodeficiency (TCR-alpha/beta deficiency and impaired T cell proliferation; B+, Ig+) TCTC7A Tetratricopeptide repeat protein 7A isoform 2 precursor 2 609332 AR Immunodeficiency with multiple intestinal atresias (T variable/absent, B+, Ig decreased) WAS Wiskott-Aldrich syndrome protein 300392 XL, GOF Wiskott-Aldrich syndrome (progressive disease with abnormal lymphocyte responses to anti-CD3, B+, Ig: decreased IgM, decreased antibody responses to polysaccharides, often increased IgA and IgE) WIPF1 WAS/WASL-interacting protein family member 1 602557 AR Wiskott-Aldrich syndrome (reduced/defective lymphocyte responses to anti-CD3; B low; Ig normal except increased IgE) XIAP (BIRC4) E3 ubiquitin-protein ligase XIAP 300079 1/million males XL X-linked lymphoproliferative syndrome (increased T cell susceptibility to apoptosis to CD95 and enhanced activation-induced cell death) ZAP70 Tyrosine-protein kinase ZAP-70 isoform 1 176947 AR Selective

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of severe combined immunodeficiency (SCID), combined immunodeficiency (CID), T-cell lymphopenia/deficiency, bare lymphocyte syndrome (BLS), or EBV-associated primary immunodeficiency (PID) Establishing a diagnosis and, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved Identifying pathogenic variants within genes known to be associated SCID, CID, T-cell lymphopenia/deficiency, BLS, or EBV-associated PID allowing for predictive testing of at-risk family members

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a
Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values:
An interpretive report will be provided.

Clinical References:

Sex Chromosome Determination, FISH, Tissue

Clinical Information: Genotypically normal females possess 2 X chromosomes (XX); genotypically normal males possess 1 X chromosome and 1 Y chromosome (XY). Determining the sex chromosome complement in a tissue specimen can be used to: -Identify opposite sex-donor cells post-transplant -Help resolve cases of suspected sample mix-up

Useful For: Identifying the sex chromosome complement in paraffin-embedded tissues

Interpretation: An interpretive report is provided.

Reference Values:
An interpretive report will be provided.

Clinical References:
Sex Hormone-Binding Globulin (SHBG), Serum

Clinical Information: Sex hormone-binding globulin (SHBG), a homodimeric 90,000 to 100,000 molecular weight glycoprotein, is synthesized in the liver. Metabolic clearance of SHBG is biphasic, with a fast initial distribution from vascular compartment into extracellular space (half-life of a few hours), followed by a slower degradation phase (half-life of several days). SHBG binds sex steroids with high affinity (KD approximately 10^{-10}M), dihydrotestosterone (DHT) -> testosterone (T) -> estrone/estradiol (E). Although each monomeric subunit contains 1 steroid binding site, the dimer tends to bind only a single sex-steroid molecule. The main function of SHBG is sex-steroid transport within the blood stream and to extravascular target tissues. SHBG also plays a key role in regulating bioavailable sex-steroid concentrations through competition of sex steroids for available binding sites and fluctuations in SHBG concentrations. Because of the higher affinity of SHBG for DHT and T, compared to E, SHBG also has profound effects on the balance between bioavailable androgens and estrogens. Increased SHBG levels may be associated with symptoms and signs of hypogonadism in men, while decreased levels can result in androgenization in women. SHBG levels in prepubertal children are higher than in adults. With the increase in fat mass during early puberty they begin to fall, a process that accelerates as androgen levels rise. Men have lower levels compared with women and nutritional status is inversely correlated with SHBG levels throughout life, possibly mediated by insulin resistance. Insulin resistance, even without obesity, results in lower SHBG levels. This is associated with increased intra-abdominal fat deposition and an unfavorable cardiovascular risk profile. In postmenopausal women, it may also predict the future development of type 2 diabetes mellitus. Androgens and norethisterone-related synthetic progesternes also decrease SHBG in women. Endogenous or exogenous thyroid hormones or estrogens increase SHBG levels. In men, there is also an age-related gradual rise, possibly secondary to the mild age-related fall in testosterone production. This process can result in bioavailable testosterone levels that are much lower than would be expected based on total testosterone measurements alone.

Useful For: Diagnosis and follow-up of women with symptoms or signs of androgen excess (eg, polycystic ovarian syndrome and idiopathic hirsutism) An adjunct in monitoring sex-steroid and anti-androgen therapy An adjunct in the diagnosis of disorders of puberty An adjunct in the diagnosis and follow-up of anorexia nervosa An adjunct in the diagnosis of thyrotoxicosis (tissue marker of thyroid hormone excess) A possible adjunct in diagnosis and follow-up of insulin resistance and cardiovascular and type 2 diabetes risk assessment, particularly in women In laboratories without access to bioavailable testosterone or equilibrium dialysis-based "true" free testosterone assays, sex hormone-binding globulin measurement is crucial in cases when assessment of the free testosterone fraction (aka free androgen index or calculated free testosterone) is required. At Mayo Medical Laboratories, both bioavailable testosterone (TTBS / Testosterone, Total and Bioavailable, Serum) and free testosterone (TGRP / Testosterone, Total and Free, Serum) measurements are available. Free testosterone (TGRP) is measured by equilibrium dialysis, obviating the need for sex hormone-binding globulin measurements to calculate free androgen fractions.

Interpretation: Many conditions of mild-to-moderate androgen excess in women, particularly polycystic ovarian syndrome, are associated with low sex hormone-binding globulin (SHBG) levels. Most of these women are also insulin resistant and many are obese. A defect in SHBG production could lead to bioavailable androgen excess, in turn causing insulin resistance that depresses SHBG levels further. There are rare cases of SHBG mutations that clearly follow this pattern. SHBG levels are typically very low in these individuals. However, in most patients, SHBG levels are mildly depressed or even within the lower part of the normal range. In these patients, the primary problem may be androgen overproduction, insulin resistance, or both. A definitive cause cannot be usually established. Any therapy that either increases SHBG levels (eg, estrogens or weight loss), reduces bioactivity of androgens (eg, androgen receptor antagonists, alpha-reductase inhibitors), or reduces insulin resistance (eg, weight loss, metformin, peroxisome proliferator-activated receptor [PPAR] gamma agonists), can be effective. Improvement is usually associated with a rise in SHBG levels, but bioavailable or free testosterone levels should also be monitored. The primary method of monitoring sex-steroid or antiandrogen therapy is direct measurement of the relevant sex-steroids and gonadotropins. However, for many synthetic androgens and estrogens (eg, ethinyl-estradiol) clinical assays are not available. In those instances, rises in SHBG levels indicate successful anti-androgen or estrogen therapy, while falls
indicate successful androgen treatment. Adult SHBG levels in boys with signs of precocious puberty support that the condition is testosterone driven, rather than representing premature adrenarche. Patients with anorexia nervosa have high SHBG levels. With successful treatment, levels start to fall as nutritional status improves. Normalization of SHBG precedes, and may be predictive of, future normalization of reproductive function. Thyrotoxicosis increases SHBG levels. In situations when assessment of true functional thyroid status may be difficult (eg, patients receiving amiodarone treatment, individuals with thyroid hormone transport-protein abnormalities, patients with suspected thyroid hormone resistance or suspected inappropriate thyroid-stimulating hormone [TSH] secretion such as a TSH-secreting pituitary adenoma), an elevated SHBG level suggests tissue thyrotoxicosis, while a normal level indicates euthyroidism or near-euthyroidism. In patients with gradual worsening of thyrotoxicosis (eg, toxic nodular goiter), serial SHBG measurement, in addition to clinical assessment, thyroid hormone, and TSH measurement, may assist in the timing of treatment decisions. Similarly, SHBG measurement may be of value in fine-tuning suppressive TSH therapy for patients with nodular thyroid disease or treated thyroid cancer. Results are not definitive in the short-term in patients receiving drugs that displace total thyroxine (T4) from albumin. SHBG is also produced by placental tissue and therefore values will be elevated during pregnancy. Reference ranges for pregnant females have not been established in our institution. In patients with known insulin resistance, "metabolic syndrome," or high risk of type 2 diabetes (eg, women with a history of gestational diabetes), low SHBG levels may predict progressive insulin resistance, cardiovascular complications, and progression to type 2 diabetes. An increase in SHBG levels may indicate successful therapeutic intervention. A genetic variant of SHBG (Asp327->Asn) introduces an additional glycosylation site in 10% to 20% of the population, resulting in significantly slower degradation. These individuals tend to have higher SHBG levels for any given level of other factors influencing SHBG.

**Reference Values:**

<table>
<thead>
<tr>
<th>Tanner Stages*</th>
<th>Mean Age</th>
<th>Reference Range (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>7.1</td>
<td>31-167</td>
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<tr>
<td>Stage II</td>
<td>11.5</td>
<td>49-179</td>
</tr>
<tr>
<td>Stage III</td>
<td>13.6</td>
<td>5.8-182</td>
</tr>
<tr>
<td>Stage IV</td>
<td>15.1</td>
<td>14-98</td>
</tr>
<tr>
<td>Stage V</td>
<td>18.0</td>
<td>10-57</td>
</tr>
</tbody>
</table>

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years. For boys, there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18. Females

<table>
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<td>Stage I</td>
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<tr>
<td>Stage II</td>
<td>10.5</td>
<td>7.7-119</td>
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<tr>
<td>Stage III</td>
<td>11.6</td>
<td>31-191</td>
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<tr>
<td>Stage IV</td>
<td>12.3</td>
<td>31-166</td>
</tr>
<tr>
<td>Stage V</td>
<td>14.5</td>
<td>18-144</td>
</tr>
</tbody>
</table>

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18. ADULTS Males: 10-57 nmol/L. Females (non-pregnant): 18-144 nmol/L.

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**SRYF 35301**

**Sex-Determining Region Y, Yp11.3 Deletion, FISH**

**Clinical Information:** This test is appropriate for individuals with a 46,XX karyotype and phenotypically normal male external genitalia, a 46,XY karyotype and phenotypically normal female external genitalia, clinical features suggestive of 46,XX testicular disorder of sex development with normal male external genitalia, and clinical features suggestive of 46,XY complete gonadal dysgenesis. The SRY (sex-determining region on the Y chromosome) gene is required for normal embryonic wolffian (male) genital development, although numerous other genes are involved in completing the process of normal male development. Some gene mutations block the action of SRY in development. Thus, a 46,XY individual with an SRY deletion or mutation will develop as a female, and a 46,XX individual with translocation of SRY to 1 X chromosome will develop as a male. Structural abnormalities of the Y chromosome result in a spectrum of abnormalities from primary infertility (male or female) to various forms of ambiguous genitalia. SRY-negative 46,XX males often have ambiguous genitalia, whereas those who are positive for SRY usually have a normal male phenotype with azoospermia. SRY-negative 46,XY females may have another mutation, such as 1 involving the SOX9 gene. We recommend conventional chromosome studies (CHRCB / Chromosome Analysis, Congenital Disorders, Blood) to detect Y chromosome abnormalities and to rule out other chromosome abnormalities or translocations, and FISH studies to detect cryptic translocations involving the SRY region that are not demonstrated by conventional chromosome studies.

**Useful For:** Detecting the deletion or addition of the SRY gene in conjunction with conventional chromosome studies (CHRCB / Chromosome Analysis, Congenital Disorders, Blood)

**Interpretation:** Any male individual with an SRY signal on a structurally normal Y chromosome is considered negative for a deletion in the region tested by this probe. Any patient with a FISH signal pattern indicating loss of the critical region will be reported as having a deletion of the regions tested by this probe. Any patient with a FISH signal on an X chromosome will be reported as having a cryptic X;Y translocation involving the critical region.

**Reference Values:**
An interpretive report will be provided.


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**SZDIA 64750**

**Sezary Diagnostic Flow Cytometry, Blood**

**Clinical Information:** Sezary syndrome is a leukemic form of cutaneous T-cell lymphoma (CTCL).

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
By definition, it is associated with systemic skin involvement (erythroderma) and the presence of at least 1000/μL of circulating cells with irregular nuclear features (Sezary cells). Morphologic assessment of the number of Sezary cells has been proven to have low reproducibility. Therefore, WHO/European Organization for Research and Treatment of Cancer (EORTC) classification of skin tumors adopted alternative methods to assess circulating T-cells in order to establish the diagnosis of Sezary syndrome. These include CD4:CD8 ratio of more than 10:1, and selective loss of CD7 and/or CD26 on 40% and 30% of the CD4-positive cell population, respectively. It is important to recognize that the later criteria (fulfilled by peripheral blood flow cytometry immunophenotyping) are relative, and not in direct correlation with absolute counts of Sezary cells defined by morphology.

**Useful For:** Identifying phenotypically aberrant T-cell population in peripheral blood as part of the diagnostic workup for Sezary syndrome. Roughly assessing the circulating tumor burden in mycosis fungoides, if the phenotype of the neoplastic cells is distinctive enough.

**Interpretation:** Sezary cells typically show loss of CD7 and/or CD26. As loss of these markers is not completely sensitive or specific for Sezary cells, and there are circulating normal CD4-positive T-cells, which usually cannot be excluded from the analysis, the WHO/European Organization for Research and Treatment of Cancer (EORTC) classification of skin tumors proposed cutoffs of 30% for CD26 loss and 40% for CD7 loss on CD4-positive T-cells as diagnostic criteria for Sezary syndrome. In addition, a CD4:CD8 ratio of greater than or equal to 10:1 in a gated T-cell population is also considered abnormal and part of the diagnostic algorithm for Sezary syndrome. In mycosis fungoides staging studies the cutoffs are even less clearly defined. The clinical outcome was worse in patients with more than 5% of circulating lymphocytes showing Sezary-like morphology. However, flow cytometry immunophenotyping is deemed useful for relative quantification of these cells only if they can be separated by aberrant expression of other surface markers. In the majority of cases, this cannot be accomplished to the proposed cutoff point (5% of circulating lymphocytes). The test will be resulted as "No phenotypically aberrant T-cell population detected" if there is no specific phenotype that allows separation of potentially abnormal CD4-positive T-cells, loss of CD26 (and/or CD7) is present in less than 30% (40%), and CD4:CD8 ratio is less than 10:1. If any of the above aberrancies are present, the test will be resulted as "Phenotypically distinct T-cell population is detected" with a description of phenotype, percentage of total CD4-positive population, and percentage of total analyzed events. In addition, the phenotype will be compared to that of any distinct T-cell population previously seen in the same patient by our laboratory.

**Reference Values:**

An interpretive report will be provided. This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and, if available, morphologic features will be provided by a board-certified hematopathologist for every case.

**Clinical References:**
the number of Sezary cells has been proven to have low reproducibility. Therefore, WHO/European Organization for Research and Treatment of Cancer (EORTC) classification of skin tumors adopted alternative methods to assess circulating T-cells in order to establish the diagnosis of Sezary syndrome. These include CD4:CD8 ratio of more than 10:1, and selective loss of CD7 and/or CD26 on 40% and 30% of the CD4-positive T-cell population, respectively. It is important to recognize that the later criteria (fulfilled by peripheral blood flow cytometry immunophenotyping) are relative, and not in direct correlation with absolute counts of Sezary cells defined by morphology.

**Useful For:** Monitoring response to therapy in patients with previously diagnosed Sezary syndrome or mycosis fungoides

**Interpretation:** Sezary cells typically show loss of CD7 and/or CD26. As loss of these markers is not completely sensitive or specific for Sezary cells, the WHO/European Organization for Research and Treatment of Cancer (EORTC) classification of skin tumors proposed cutoffs of 30% for CD26 loss and 40% for CD7 loss on CD4-positive T-cells, as diagnostic criteria for Sezary syndrome. In addition, CD4:CD8 ratio of greater than or equal to 10:1 in a gated T-cell population is also considered abnormal, and part of diagnostic algorithm for Sezary syndrome. In mycosis fungoides staging studies the cutoffs are even less clearly defined. The clinical outcome was worse in patients with more than 5% of circulating lymphocytes showing Sezary-like morphology. However, flow cytometry immunophenotyping is deemed useful for relative quantification of these cells only if they can be separated by aberrant expression of other surface markers. In majority of cases, this cannot be accomplished to the proposed cutoff point (5% of circulating lymphocytes). The test will be resulted as "No phenotypically aberrant T-cell population detected" if there is no specific phenotype that allows separation of potentially abnormal CD4-positive T-cells, loss of CD26 (and/or CD7) is present in less than 30% (40%), and CD4:CD8 ratio is less than 10:1. If any of the above aberrancies are present, the test will be resulted as "Phenotypically distinct T-cell population is detected" with a description of phenotype, percentage of total CD4-positive population and percentage of total analyzed events. In addition, the phenotype will be compared to that of any distinct T-cell population previously seen in the same patient by our laboratory.

**Reference Values:**
An interpretive report will be provided. This test will be processed as a laboratory consultation. An interpretation of the immunophenotypic findings and, if available, morphologic features will be provided by a board-certified hematopathologist for every case.

**Clinical References:**

**SF-1 Immunostain, Technical Component Only**

**Clinical Information:** SF-1, also known as steroidogenic factor 1, is a transcription factor involved in the development of the anterior pituitary and is useful in the classification of pituitary adenomas. Expression of SF-1 is observed in gonadotropic hormone producing tumors (follicular stimulating or luteinizing hormone).

**Useful For:** Classification of pituitary adenomas
**Interpretation:** The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Reference Values:**

N/A

**Clinical References:**

**Sheep Wool, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

STFRP 35148

Shiga Toxin, Molecular Detection, PCR, Feces

Clinical Information: Shiga toxins (also known as Shiga-like toxins, Vero toxins, or Vero-like toxins) are encoded by some strains of Escherichia coli, most notably O157:H7. Shiga toxin can also be produced by other serogroups of enterohemorrhagic E coli (EHEC), as well as Shigella dysenteriae type 1. Generally, Shiga toxin-producing organisms cause bloody diarrhea, although this is not universal. Unlike some bacterial gastrointestinal infections, antimicrobial therapy is contraindicated, as antimicrobials may exacerbate disease. Treatment is primarily supportive (eg, hydration). A complication of infection by an organism producing Shiga toxin is hemolytic uremic syndrome (HUS). The percentage of people that develop HUS varies among outbreaks of E coli O157:H7, but generally ranges from 3% to 20%. HUS is characterized by a triad of findings: hemolytic anemia, thrombocytopenia, and kidney failure. Most people recover completely, however, some require permanent dialysis, and some die as a result of complications. Several diagnostic methods available for the detection of EHEC lack sensitivity, are labor intensive, or have a long turnaround time. There are more than 160 serogroups of EHEC; the first serogroup to be associated with HUS was O157:H7. This is also the serogroup that is most commonly implicated in outbreaks. EHEC O157:H7 is detectable as nonfermenting colonies when cultured on sorbitol MacConkey (SMAC) agar, but the majority of non-O157:H7 Shiga toxin-producing E coli strains ferment sorbitol and, therefore, are undetectable by this method. The Vero cell line is susceptible to the Shiga toxin, but the assay can take up to 48 hours and is nonspecific. Commercial enzyme-linked immunosorbent assay (ELISA) antigen detection kits have a sensitivity of 90% when compared to culture, but an overnight enrichment step is necessary for adequate sensitivity. PCR detection of stx, the gene encoding Shiga toxin, directly from stool specimens is a sensitive and specific technique, providing same-day results. PCR assay identifies non-O157:H7 Shiga toxin-producing bacteria, extending the utility beyond strains identifiable on SMAC agar.

Useful For: Sensitive, specific, and rapid detection of the presence of Shiga toxin-producing organisms such as Escherichia coli O157:H7 and Shigella dysenteriae type 1 in stool

Interpretation: A positive PCR result indicates the likely presence of Shiga toxin-producing Escherichia coli in the specimen. Although Shigella dysenteriae serotype 1 may produce a positive result, it is extremely rare in the United States. A negative result indicates the absence of detectable Shiga toxin DNA in the specimen, but does not rule out the presence of Shiga toxin-producing E coli, as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of the Shiga toxin gene in quantities less than the limit of detection of the assay. Shiga toxins are encoded on mobile genetic elements and can theoretically be lost by their bacterial host.

Reference Values: Not applicable

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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SCADZ 35544

Short-Chain Acyl-CoA Dehydrogenase (SCAD) Deficiency, Full Gene Analysis

Clinical Information: Short-chain acyl-CoA dehydrogenase (SCAD) catalyzes the first step in the mitochondrial beta-oxidation of fatty acids with a chain length of 6 to 4 carbons. SCAD deficiency is a rare autosomal recessive condition. The clinical phenotype of SCAD shows considerable variability and is incompletely defined. Of those reported cases, hypoglycemia, developmental delay, and muscle hypotonia are the most common indicated features. The diagnosis of SCAD deficiency is challenging and should be based on the clinical presentation, 2 or more findings of ethylmalonic aciduria, and determination of fatty acid flux in fibroblasts indicating deficient SCAD activity. Molecular genetic analysis of the gene associated with SCAD (ACADS) may confirm the biochemical phenotype of SCAD deficiency. The first step in evaluation for SCAD deficiency is identification of 2 or more findings of ethylmalonic aciduria, as determined by either OAU / Organic Acids Screen, Urine or ACYLG / Acylglycines, Quantitative, Urine. Ethylmalonic aciduria is a common, although not specific, laboratory finding in patients with SCAD deficiency. Determination of fatty acid flux in fibroblasts (FAO / Fatty Acid Oxidation Probe Assay,
Fibroblast Culture) is warranted for an individual with 2 or more findings of ethylmalonic aciduria. DNA sequencing of the ACADS gene is typically utilized only when SCAD deficiency is identified through biochemical analysis. The ACADS gene, associated with SCAD deficiency, is located on chromosome 12q22 and consists of 10 exons. Molecular genetic studies revealed that some patients carry ACADS gene mutations that cause complete absence of SCAD activity, while others carry ACADS gene variants (511C->T;625G->A) that may confer disease susceptibility only in association with other factors. The allele frequencies in the general population of the 511C->T and 625G->A gene variants are 3% and 22%, respectively. The presence of 2 of these gene variants is not considered an independent diagnostic marker for SCAD deficiency. Although further investigation is needed, it is most likely that these variants are not clinically significant. Identification of 2 ACADS gene mutations that cause complete absence of SCAD activity alone is not sufficient to explain or determine possible clinical phenotype or prognosis. The clinical significance of carrying 2 mutations is often uncertain. Therefore, the results of ACADS gene sequencing for SCAD deficiency should be interpreted in light of the clinical presentation and biochemical findings in each case.

**Useful For:** Preferred molecular analysis to confirm a diagnosis of short-chain acyl-CoA dehydrogenase deficiency (as a follow-up to the biochemical analyses only)

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FSHOX**
**SHOX-DNA-DxTM**
**Reference Values:**
Testing is complete. Report has been attached in MayoAccess.

**FSHRG**
**Shrimp IgG**
**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation* 2.0 Upper Limit of Quantitation** 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.
**Shrimp, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


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**Signal Transducer and Activator of Transcription 6 (STAT6), Technical Component Only**

**Clinical Information:** Signal transducer and activator of transcription 6 (STAT6) is a signal transducer/transcription activator expressed in the cytoplasm of various normal tissues including bladder epithelium, bronchial epithelium, and epidermis. NAB2-STAT6 fusions have recently been described in the majority of solitary fibrous tumors (SFT), and lead to aberrant strong nuclear STAT6 staining.

**Useful For:** Aids in distinguishing solitary fibrous tumor from morphologic mimics

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is...
required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

### FSIL 80771

**Silicon, Serum/Plasma**

**Reference Values:**

- Reporting limit determined each analysis.

- Generally: Less than 0.05 mg/dL
- Silicon concentrations are influenced by diet, especially vegetable intake.

### SILK 82771

**Silk, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Silver Birch, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tbody>
</table>

Reference values apply to all ages.

Sinemet, Serum/Plasma

Reference Values:
Reporting limit determined each analysis.

Levodopa
Synonym(s): Sinemet Constituent

Carbidopa
Synonym(s): Sinemet Constituent

Following a single oral dose of 100 mg Levodopa and 25 mg Carbidopa (conventional Sinemet tablet):
Approximately 0.3 mcg Levodopa/mL and 0.05 mcg Carbidopa/mL plasma at 1 hour post dose.
Average steady-state trough plasma levels in elderly patients following a regimen of Sinemet CR (50 mg Carbidopa and 200 mg Levodopa sustained release tablets) three times daily:
0.16 mcg Levodopa/mL
0.07 mcg Carbidopa/mL

Sirolimus, Blood

Clinical Information: Sirolimus is a macrolide antibiotic, isolated from Streptomyces hygroscopicus, with potent effects including suppression of T- and B-cell proliferation and antineoplastic and antifungal activity. It inhibits the protein kinase mTOR to arrest the cell cycle; it has no effects on calcineurin and, therefore, can be used in addition to cyclosporine or tacrolimus, or as a substitute in patients intolerant to these drugs. Sirolimus is metabolized by CYP3A4, thus, blood concentrations are affected by drugs that inhibit or induce this enzyme. The pharmacokinetic interaction between sirolimus and cyclosporine or tacrolimus increases both therapeutic immunosuppression and the toxicity of these agents; lower doses are required with combined use. Adverse effects of sirolimus are generally concentration dependent, making therapeutic drug monitoring essential. Trough sirolimus concentrations are generally measured every 5 days. Target concentrations vary depending on concomitant therapy, time posttransplant, the desired degree of immunosuppression, and adverse effects. When given with cyclosporine or tacrolimus, the therapeutic range for sirolimus is generally between 4 and 12 ng/mL with minimal added benefit for concentrations >10 ng/mL. When sirolimus is given without calcineurin inhibitors, higher trough levels are needed; usually 12 to 20 ng/mL, but occasionally up to 20 to 30 ng/mL.

Useful For: Monitoring whole blood sirolimus concentration during therapy, particularly in individuals coadministered CYP3A4 substrates, inhibitors, or inducers Adjusting dose to optimize immunosuppression while minimizing toxicity Evaluating patient compliance

Interpretation: Most individuals display optimal response to sirolimus with trough whole blood levels 4 to 20 ng/mL. Preferred therapeutic ranges may vary by transplant type, protocol, and comediations. Therapeutic ranges are based on specimens drawn at trough (ie, immediately before a scheduled dose). Blood drawn at other times will yield higher results. The assay is specific for sirolimus; it does not cross-react with cyclosporine, cyclosporine metabolites, tacrolimus, tacrolimus metabolites, or sirolimus metabolites. Results by liquid chromatography with detection by liquid chromatography-tandem mass spectrometry are approximately 30% less than by immunoassay.

Reference Values:
4-20 ng/mL (Trough)

Target steady-state trough concentrations vary depending on the type of transplant, concomitant immunosuppression, clinical/institutional protocols, and time post-transplant. Results should be interpreted in conjunction with this clinical information and any physical signs/symptoms of rejection/toxicity.

Clinical References: 1. Kahan BD: Ten years of mTOR inhibitor therapy. Transplant Proc
Skeletal Muscle Channelopathy Panel (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

Slide Review in Molecular Genetics (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

Sm Antibodies, IgG, Serum

Clinical Information: Sm is a small nuclear ribonucleoprotein composed of several protein autoantigens designated B, B1, D, E, F, and G, which range in size from 11 kD to 26 kD. Sm antibodies are specific for lupus erythematosus (LE) and occur in approximately 30% of LE patients. The levels of Sm antibodies remain relatively constant over time in patients with LE and are usually found in patients that also have RNP antibodies. (1,2) Sm is 1 of 4 autoantigens commonly referred to as extractable nuclear antigens (ENAs). The other ENAs are RNP, SS-A/Ro, and SS-B/La. Each ENA is composed of 1 or more proteins associated with small nuclear RNA species (snRNP) ranging in size from 80 to approximately 350 nucleotides. Antibodies to ENAs are common in patients with connective tissue diseases (systemic rheumatic diseases) including LE, mixed connective tissue disease, Sjogren syndrome, scleroderma (systemic sclerosis), and polymyositis/dermatomyositis. See Connective Tissue Disease Cascade (CTDC) in Special Instructions.

Useful For: Evaluating patients with signs and symptoms of a connective tissue disease in whom the test for antinuclear antibodies is positive

Interpretation: A positive result for anti-Sm antibodies is consistent with a diagnosis of lupus erythematosus.

Reference Values:
<1.0 U (negative)
> or =1.0 U (positive)
Reference values apply to all ages.


SMAD4 Gene, Full Gene Analysis

Clinical Information: Juvenile polyposis syndrome (JPS) is a rare hereditary cancer predisposition syndrome caused by mutations in the SMAD4 or BMPR1A genes. JPS is characterized by the presence of multiple histologically defined juvenile polyps in the upper and/or lower gastrointestinal (GI) tract and an increased risk for GI cancers. Age of onset for cancer development is typically in the second or third
decade of life, although some patients present with a more severe infantile-onset form of the disease. JPS is inherited in an autosomal dominant fashion, although a significant proportion of probands have no family history. Approximately 50% of patients with JPS have an identifiable mutation in the SMAD4 or BMPR1A genes. Of note, some patients with mutations in the SMAD4 gene exhibit a combined juvenile polyposis/hereditary hemorrhagic telangiectasia phenotype (JP/HHT). Clinical features of HHT include development of arteriovenous malformations (AVMs) of the skin, mucosa, and visceræ; spontaneous, recurrent epistaxis (nosebleeds); as well as additional complications such as transient ischemic attacks, embolic stroke, heart failure, cerebral abscess, massive hemoptyisis, massive hemotherax, seizure, and cerebral hemorrhage.

**Useful For:** Confirmation of juvenile polyposis syndrome or juvenile polyposis/hereditary hemorrhagic telangiectasia for patients with clinical features This test should be ordered only for individuals with symptoms suggestive of juvenile polyposis syndrome or juvenile polyposis/hereditary hemorrhagic telangiectasia. Asymptomatic patients with a family history of juvenile polyposis syndrome or juvenile polyposis/hereditary hemorrhagic telangiectasia should not be tested until a mutation has been identified in an affected family member.

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity, and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Small Lymphocytic Lymphoma, FISH, Tissue**

**Clinical Information:** Small lymphocytic lymphoma (SLL) is the nonleukemic form of chronic lymphocytic leukemia (CLL), the most common adult leukemia in North America. The most common cytogenetic abnormalities detected in CLL are deletions of 6q, 11q, 13q, and 17p, trisomy 12, and the occasional occurrence of IGH translocations at 14q32. Cytogenetics has proven to be a reliable predictor of outcome for patients with CLL. It is unknown if SLL has the same prognostic significance when these genetic abnormalities are observed. This FISH test detects an abnormal clone in approximately 65% of patients with SLL. Patients with t(11;14)(q13;q32) associated with CCND1/IGH fusion, have mantle cell lymphoma which can be distinguished from SLL and other B-cell lymphomas with this assay. Patients with t(14;18)(q32;q21) or t(14;19)(q32;q13.3) may have an atypical form of SLL or another low-grade B-cell lymphoma.

**Useful For:** Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with small lymphocytic lymphoma (SLL) and other low-grade B-cell lymphomas Distinguishing patients with 11;14 translocations who have mantle cell lymphoma from patients who have SLL

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. A positive result is not diagnostic for small
lymphocytic lymphoma, but may provide relevant prognostic information. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Smith-Lemli-Opitz Screen, Plasma**

**Clinical Information:** Cholesterol plays an essential role in many cellular and developmental processes. In addition to its role as a membrane lipid, it is the precursor to numerous molecules that play important roles in cell growth and differentiation, protein glycosylation, and signaling pathways. The biosynthesis of cholesterol and its subsequent conversion to other essential compounds is complex, involving a number of intermediates and enzymes. Disorders that result from a deficiency of these enzymes lead to an accumulation of specific intermediates and inhibit the formation of important biomolecules. Clinical findings common to cholesterol biosynthesis disorders include congenital skeletal malformations, dysmorphic facial features, psychomotor retardation, and failure to thrive. Smith-Lemli-Opitz syndrome (SLO) is an autosomal recessive disorder caused by mutations in the DHCR7 gene leading to a deficiency of the 7-dehydrocholesterol reductase enzyme. It is characterized biochemically by markedly increased plasma concentrations of 7-dehydrocholesterol (7-DHC) and 8-dehydrocholesterol (8-DHC) levels. Clinically, features can include microcephaly, growth retardation, developmental delay, dysmorphic facial features, cleft palate, limb abnormalities (especially 2-3 syndactyly of the toes and postaxial polydactyly), and heart and kidney malformations. However, the clinical spectrum ranges from mild to severe with some mildly affected individuals presenting with only 2 to 3 toe syndactyly and mild cognitive impairment. The reported incidence is between 1 in 10,000 and 1 in 60,000, but it may be more prevalent due to underdiagnosis of mildly affected individuals. Other disorders of cholesterol biosynthesis, including desmosterolosis (desmosterol reductase deficiency) and sitosterolemia, may present with similar manifestations. These disorders can be detected biochemically by performing a quantitative profile of plasma sterols (STER / Sterols, Plasma).

**Useful For:** Diagnosis of Smith-Lemli-Opitz syndrome (7-dehydrocholesterol reductase deficiency)

**Interpretation:** Elevated plasma concentrations of 7-dehydrocholesterol (7-DHC) and 8-dehydrocholesterol (8-DHC) are highly suggestive of a biochemical diagnosis of Smith-Lemli-Opitz (SLO). Mild elevations of these cholesterol precursors can be detected in patients with hypercholesterolemia and patients treated with haloperidol. However, the 7-DHC to cholesterol ratio is only elevated in SLO patients.

**Reference Values:**
Negative (reported as positive or negative)
Quantitative results are provided when positive.

**Clinical References:**
Smooth Muscle Antibodies, Serum

**Clinical Information:** Sera from patients with autoimmune chronic active hepatitis contain antibodies to smooth muscle antigens that are detectable by indirect immunofluorescence on substrates that contain smooth muscle. The antibodies are predominantly of the IgG isotype. Other diseases in this differential diagnosis group include primary biliary cirrhosis, chronic viral hepatitis, and alcoholic chronic hepatitis.

**Useful For:** Evaluating patients with chronic liver disease in whom the diagnosis of chronic active autoimmune hepatitis is suspected

**Interpretation:** Antibody titers in the range of 80 to 320 occur commonly in patients with active chronic hepatitis; lower titers (usually <80) may occur in the other conditions mentioned earlier.

**Reference Values:**
- Negative
  - If positive, results are titered.
  - Reference values apply to all ages.

**Clinical References:** Czaja AJ, Homburger HA: Autoantibodies in liver disease. Gastroenterology 2001;120:239-249

Smoothelin Immunostain, Technical Component Only

**Clinical Information:** Smoothelin is a smooth muscle-specific marker expressed only in terminally differentiated smooth muscle cells as part of the cytoskeleton. It is expressed normally in the smooth muscle of the muscularis of the bowel as well as in smooth muscle in other organs.

**Useful For:** Distinguishing muscularis mucosae from muscularis propria

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Smut Corn (Ustilago maydis) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35–0.69 Low Positive 2 0.70–3.49 Moderate Positive 3 3.50–17.49 Positive 4 17.50–49.99 Strong Positive 5 50.00–99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

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**Snail, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35–0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70–3.49</td>
</tr>
<tr>
<td>3</td>
<td>3.50–17.4</td>
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<td>17.5–49.9</td>
</tr>
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<td>5</td>
<td>50.0–99.9</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Sodium, 24 Hour, Urine**

**Clinical Information:** Sodium (Na+) is the primary extracellular cation. Sodium is responsible for almost one half the osmolality of the plasma and, therefore, plays a central role in maintaining the normal
distribution of water and the osmotic pressure in the extracellular fluid compartment. The amount of Na+ in the body is a reflection of the balance between Na+ intake and output. The normal daily diet contains 8 to 15 grams of sodium chloride (NaCl) which is nearly completely absorbed from the gastrointestinal tract. The body requires only 1 to 2 mmol/d, and the excess is excreted by the kidneys, which are the ultimate regulators of the amount of Na+ (and thus water) in the body. Sodium is freely filtered by the glomeruli. Approximately 70% to 80% of the filtered Na+ is actively reabsorbed in the proximal tubules with chloride and water passively following in an iso-osmotic and electrically neutral manner. Another 20% to 25% is reabsorbed in the loop of Henle along with chloride and more water. In the distal tubules, interaction of the adrenocortical hormone aldosterone with the coupled sodium-potassium and sodium-hydrogen exchange systems directly results in the reabsorption of Na+ and indirectly of chloride from the remaining 5% to 10% of the filtered load. It is the regulation of this latter fraction of filtered Na+ that determines the amount of Na+ excreted in the urine.

**Useful For:** Assessing acid-base balance, water balance, water intoxication, and dehydration

**Interpretation:** Urinary sodium (Na+) excretion varies with dietary intake, and there is a large diurnal variation with the rate of Na+ excretion during the night being only 20% of the peak rate during the day. Sodium may be lost in the kidneys as a result of diuretic therapy, salt-losing nephropathies, or adrenal insufficiency, with the urinary Na+ concentration usually more than 20 mEq/L. In these hypovolemic states, urine Na+ values <10 mEq/L indicate extrarenal Na+ loss. In hypervolemic states, a low urine Na+ (<10 mEq/L) may indicate nephrotic syndrome in addition to non-renal causes.

**Reference Values:**
41-227 mmol/24 hours


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**NABF**

**Sodium, Body Fluid**

**Reference Values:**
Not applicable

**Clinical References:** Tietz Textbook of Clinical Chemistry. Edited by Burtis and Ashwood. Philadelphia, WB Saunders Co, 1994

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**RNAUR**

**Sodium, Random, Urine**

**Clinical Information:** Sodium (Na+) is the primary extracellular cation. Na+ is responsible for almost one-half the osmolality of the plasma and, therefore, plays a central role in maintaining the normal distribution of water and the osmotic pressure in the extracellular fluid compartment. The amount of Na+ in the body is a reflection of the balance between Na+ intake and output. The normal daily diet contains 8 to 15 grams of sodium chloride (NaCl), which is nearly completely absorbed from the gastrointestinal tract. The body requires only 1 to 2 mmol/day, and the excess is excreted by the kidneys, which are the ultimate regulators of the amount of Na+ (and thus water) in the body. Na+ is freely filtered by the glomeruli. Approximately 70% to 80% of the filtered Na+ is actively reabsorbed in the proximal tubules with chloride and water passively following in an iso-osmotic and electrically neutral manner. Another 20% to 25% is reabsorbed in the loop of Henle along with chloride and more water. In the distal tubules, interaction of the adrenocortical hormone aldosterone with the coupled sodium-potassium and sodium-hydrogen exchange systems directly results in the reabsorption of Na+ and indirectly of chloride from the remaining 5% to 10% of the filtered load. It is the regulation of this latter fraction of filtered Na+ that determines the amount of Na+ excreted in the urine.

**Useful For:** Assessing acid-base balance, water balance, water intoxication, and dehydration

**Interpretation:** Urinary sodium (Na+) excretion varies with dietary intake, and there is a large diurnal variation with the rate of Na+ excretion during the night being only 20% of the peak rate during the day. Na+ may be lost in the kidneys as a result of diuretic therapy, salt-losing nephropathies, or
adrenal insufficiency, with the urinary Na+ concentration usually more than 20 mEq/L. In these hypovolemic states, urine Na+ values less than 10 mEq/L indicate extrarenal Na+ loss. In hypervolemic states, a low urine Na+ (<10 mEq/L) may indicate nephrotic syndrome in addition to nonrenal causes.

**Reference Values:**
No established reference values.


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**Sodium, Serum**

**Clinical Information:** Sodium is the primary extracellular cation. Sodium is responsible for almost one half the osmolality of the plasma and therefore plays a central role in maintaining the normal distribution of water and the osmotic pressure in the extracellular fluid compartment. The amount of sodium in the body is a reflection of the balance between sodium intake and output. Hyponatremia (low sodium) is a predictable consequence of decreased intake of sodium, particularly that precipitated or complicated by unusual losses of sodium from the gastrointestinal tract (eg, vomiting and diarrhea), kidneys or sweat glands. Renal loss may be caused by inappropriate choice, dose or use of diuretics; by primary or secondary deficiency of aldosterone and other mineralocorticoids; or by severe polyuria. It is common in metabolic acidosis. Hyponatremia also occurs in nephrotic syndrome, hypoproteinemia, primary and secondary adrenocortical insufficiency and congestive heart failure. Symptoms of hyponatremia are a result of brain swelling and range from weakness to seizures, coma and death. Hypernatremia (high sodium) is often attributable to excessive loss of sodium-poor body fluids. Hypernatremia is often associated with hypercalcemia and hypokalemia and is seen in liver disease, cardiac failure, pregnancy, burns, and osmotic diuresis. Other causes include decreased production of ADH or decreased tubular sensitivity to the hormone (ie, diabetes insipidus), inappropriate forms of parenteral therapy with saline solutions, or high salt intake without corresponding intake of water. Hypernatremia occurs in dehydration, increased renal sodium conservation in hyperaldosteronism, Cushing’s syndrome, and diabetic acidosis. Severe hypernatremia may be associated with volume contraction, lactic acidosis and increased hematocrit. Symptoms of hypernatremia range from thirst to confusion, irritability, seizures, coma and death.

**Useful For:** Sodium assays are important in assessing acid-base balance, water balance, water intoxication, and dehydration.

**Interpretation:** Symptoms of hyponatremia depend primarily upon the rate of change in sodium concentration, rather than the absolute level. Typically, sodium values <120 mEq/L result in weakness; values <100 mEq/L in bulbar or pseudobulbar palsy; and values between 90 and 105 mEq/L in severe signs and symptoms of neurological impairment. Symptoms associated with hypernatremia depend upon the degree of hyperosmolality present.

**Reference Values:**
> or =12 months: 135-145 mmol/L

Reference values have not been established for patients that are less than 12 months of age.

**Clinical References:** Tietz Textbook of Clinical Chemistry. Edited by CA Burtis, ER Ashwood. WB Saunders Company. Philadelphia, PA, 1994

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**Sole, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and
clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
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<tr>
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<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**CAPN 35594**

**Solid Tumor-Targeted Cancer Gene Panel by Next-Generation Sequencing**

**Clinical Information:** Targeted cancer therapies are defined as antibody or small molecule drugs that block the growth and spread of cancer by interfering with specific cell molecules involved in tumor growth and progression. Multiple targeted therapies have been approved by the United States Food and Drug Administration (FDA) for treatment of specific cancers. Molecular genetic profiling is often needed to identify targets amenable to targeted therapies and to minimize treatment costs and therapy-associated risks. Next-generation sequencing has recently emerged as an accurate, cost-effective method to identify mutations across numerous genes known to be associated with response or resistance to specific targeted therapies. This test is a single assay that uses formalin-fixed paraffin-embedded tissue to assess for common mutations in 50 genes known to be associated with cancer. The results of this test can be useful for assessing prognosis and guiding treatment of individuals with solid tumors. These data can also be used to help determine clinical trial eligibility for patients with mutations in genes not amenable to current FDA-approved targeted therapies. See Targeted Gene Regions Interrogated by Solid Tumor Targeted Cancer Gene Panel by Next-Generation Sequencing in Special Instructions for details regarding the targeted gene regions identified by this test.

**Useful For:** Identifying solid tumors that may respond to targeted therapies by assessing multiple gene targets simultaneously Identifying specific mutations within genes known to be associated with response or resistance to specific cancer therapies Identifying mutations that may help determine...
prognosis for patients with solid tumors Assisting in establishing a diagnosis (eg, KIT and PDGFRA alterations for gastrointestinal stromal tumors)

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.


**FSFM**

**Soluble Fibrin Monomer**

**Reference Values:**
Negative

**FSLAA**

**Soluble Liver Antigen (SLA) Autoantibody**

**Clinical Information:** Anti-soluble liver antigen antibodies are detected in 10-30% of patients with type 1 autoimmune hepatitis (AIH), but not in patients with type 2 AIH, primary sclerosing cholangitis or primary biliary cirrhosis. The antibody is directed against a UGA suppressor tRNA associated protein. In some patients with AIH, this antibody may be the only autoantibody detected by current assays.

**Reference Values:**
Reference Range: Negative 0.0 – 20.0 U
Equivocal 20.1 – 24.9 U
Positive >25.0 U

Antibodies to soluble liver antigen (SLA) appear to be directed against the UGA-suppressor tRNA associated protein. These antibodies are highly specific for autoimmune hepatitis (AIH) and may rarely, be the only autoantibodies detected in serum from such patients. Antibodies to SLA are most closely associated with AIH type 1; the presence of these antibodies in patients with cryptogenic hepatitis suggests that these patients may have AIH type 1.

Anti-SLA antibodies may be detected in some patients with the primary biliary cirrhosis-AIH overlap syndrome, but not in healthy controls.

**STFR**

**Soluble Transferrin Receptor (sTfR), Serum**

**Clinical Information:** Iron uptake into cells is mediated through internalizing iron-transferrin complexes. The iron-transferrin complex binds to transferrin receptors present on the external face of the plasma membrane, and is internalized through endosomes with ultimate release of iron into the cytoplasm. Plasma membrane-bound transferrin receptor is released by proteolytic cleavage of the extracellular domain, resulting in the formation of a truncated soluble transferrin receptor (sTfR) that circulates freely in the blood. The concentration of sTfR is an indicator of iron status. Iron deficiency causes overexpression of transferrin receptor and sTfR levels, while iron repletion results in decreased sTfR levels. While ferritin measurement is the accepted method for assessment of iron deficiency, ferritin is an acute-phase reactant and elevates in response to processes that do not correlate with iron status, including inflammation, chronic disease, malignancy, and infection. sTfR is not an acute-phase reactant and the interpretation of iron status using sTfR measurement is not affected by these confounding pathologies.

**Useful For:** Evaluation of suspected iron deficiency in patients who may have inflammation, infection,
or chronic disease and other conditions in which ferritin concentration does not correlate with iron status, including: -Cystic fibrosis patients who frequently have inflammation or infections(1-2) -Evaluating insulin-dependent diabetics who may have iron-deficiency resulting from gastric autoimmunity and atrophic gastritis(3)

**Interpretation:** Soluble transferrin receptor (sTfR) concentrations are inversely related to iron status; sTfR elevates in response to iron deficiency and decreases in response to iron repletion.

**Reference Values:**
1.8-4.6 mg/L

It is reported that African Americans may have slightly higher values.

**Clinical References:**

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**SLC1V 97399**

**Solute Carrier Organic Anion Transporter Family Member 1B1 (SLCO1B1) Genotype, Statin**

**Clinical Information:** The most common adverse drug reaction associated with statins is skeletal muscle toxicity, which can include myalgia (with and without elevated creatine kinase levels), muscle weakness, muscle cramps, myositis, and rhabdomyolysis. Rhabdomyolysis, while rare, is of clinical concern because of the risk for death as a result of cardiac arrhythmia, renal failure, and disseminated intravascular coagulation. While the underlying causes of statin-associated myopathy are not known, several hypotheses have been formulated, including those related to the biochemical pathway of cholesterol synthesis inhibition and statin metabolism. SLCO1B1 encodes the organic anion-transporting polypeptide 1B1 (OATP1B1) influx transporter located on the basolateral membrane of hepatocytes. OATP1B1 facilitates the hepatic uptake of statins as well as other endogenous compounds (eg, bilirubin). Changes in the activity of this transporter (eg, through genetic variations or drug-drug interactions) can increase the severity of statin-associated myopathy (ie, statin intolerance). SLCO1B1 rs4149056 (c.521T->C: p.V174A), which is found in *5, *15, and *17, interferes with localization of the transporter to the plasma membrane, and can lead to increased systemic statin concentrations. All statins are substrates of OATP1B1, but the association of SLCO1B1 c.521T>C with statin intolerance varies depending on statin and dose, and is most pronounced with higher doses of simvastatin therapy. A case-control study of simvastatin-induced myopathy observed an odds ratio (OR) for myopathy of 4.5 for *5 heterozygotes and 16.9 for *5 homozygotes (compared to individuals who did not carry *5) among patients receiving high-dose (80 mg/day) simvastatin therapy. A dose relationship was also demonstrated in a replication cohort of patients taking 40 mg/day simvastatin with a relative risk of 2.6 per copy of the *5 allele. While the SLCO1B1 c.521T->C genotype has also been shown to affect systemic exposure of other statins (eg, atorvastatin, pravastatin, rosuvastatin) in addition to simvastatin, there is less evidence demonstrating a clinical association between the SLCO1B1 genotype and myopathy with statins other than simvastatin. SLCO1B1 rs4149015 (c.-910G->A), which is found in *17 and *21, is associated with increased pravastatin blood levels and a reduced lipid lowering effect, but has not been associated with statin-induced myopathy or rhabdomyolysis. Frequency of the SLCO1B1 alleles varies across different racial and ethnic groups.

**Useful For:** Predicting risk for statin-associated myopathy in patients beginning statin therapy, especially simvastatin therapy Determining a potential statin lipid lowering response, especially when using pravastatin
**Interpretation:** An interpretive report will be provided. For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FSOMA 90172**

**Somatostatin**

**Clinical Information:** Somatostatin is a cyclic peptide originally isolated from sheep hypothalami and shown to inhibit the release of Growth Hormone. Somatostatin is present primarily in three main forms: a 14 amino acid peptide, a 28 amino acid peptide (“Big” Somatostatin), and a 12,000 molecular weight ProSomatostatin. This assay measures only the 14 amino acid form of Somatostatin. All three forms of Somatostatin have similar biological properties and overall potencies. Somatostatin is a physiological regulator of islet cell and gastrointestinal functions, and is a suppressor of many pituitary hormones including Growth Hormone, Prolactin, and Thyrotropin (TSH). Somatostatin levels are often elevated in diabetics, but the levels return to normal upon correction of the hormonal and metabolic deficiencies present. In many cases of APUDomas including VIPoma, Insulinoma, Glucagonoma, and Gastrinoma, elevated levels of Somatostatin are found.

**Reference Values:**
Up to 25 pg/ml

This test was developed and its performance characteristics determined by Inter Science Institute. It has not been cleared or approved by the US Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

**SOMAT 70553**

**Somatostatin (SOMATO) Immunostain, Technical Component Only**

**Clinical Information:** Somatostatin is a cyclic polypeptide hormone originally isolated from the hypothalamus and characterized by its ability to inhibit the release of growth hormone from the pituitary. In the digestive system, somatostatin production occurs in the intrinsic nerves of the intestinal wall, endocrine cells of the digestive mucosa, and in the D-cells of pancreatic islets. Antibodies to somatostatin can be used to characterize pancreatic islet cell tumors or other neuroendocrine tumors.

**Useful For:** Aids in the characterization of pancreatic islet cell tumors or other neuroendocrine tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.
**Clinical References:**

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**SSTR2**

**Somatostatin Receptor 2 (SSTR2), Immunostain, Technical Component Only**

**Clinical Information:** Somatostatin receptor 2 (SSTR2) is expressed in the secretory cells of the pancreas and the neurons of the central nervous system. SSTR2 is overexpressed in neuroendocrine tumors (NET) and can help predict response to targeted radiopeptide therapy. SSTR2 expression can also play a role in guiding imaging studies and treatment choice.

**Useful For:** Aids in the identification of neuroendocrine tumors

**Interpretation:** The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**FSOTA**

**Sotalol (Betapace)**

**Reference Values:**
Reference Range: 500 - 4000 ng/mL

Serum Sotalol concentrations producing beta-blockade:
500 - 4000 ng/mL

Toxic range has not been established.

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**SOX10**

**SOX10 Immunostain, Technical Component Only**

**Clinical Information:** SOX10 is a nuclear transcription factor that plays an important role in schwannian and melanocytic cell differentiation, and has been shown to be a useful marker in the diagnosis of melanocytic and schwannian tumors. SOX10 is expressed in benign melanocytic naevi and melanomas, including desmoplastic melanoma and spindle cell melanoma. It is also expressed by tumors with schwannian differentiation, including malignant peripheral nerve sheath tumors, Schwannomas, and neurofibromas. SOX10 is expressed in normal tissues, including Schwann cells, melanocytes, and myoepithelial cells of salivary, bronchial, and mammary glands.
Useful For: Identification of malignant melanomas

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


SOX11 Immunostain, Bone Marrow, Technical Component Only

Clinical Information: SOX11 is a transcription factor involved in embryonic neurogenesis and tissue remodeling. Nuclear SOX11 is expressed in most B- and T-lymphoblastic leukemia and lymphomas and a proportion of Burkitt lymphomas, but only weakly expressed in some hairy cell leukemias. Mantle cell lymphomas (MCL) show SOX11 expression and it has been suggested to correlate with overall survival.

Useful For: Identification of mantle cell lymphomas

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request, call 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical Information: SOX11 is a transcription factor involved in embryonic neurogenesis and tissue remodeling. Nuclear SOX11 is expressed in most B- and T-lymphoblastic leukemia/lymphomas and a proportion of Burkitt lymphomas, but only weakly expressed in some hairy cell leukemias. Mantle cell lymphomas (MCL) show SOX11 expression and it has been suggested to correlate with overall survival.

Useful For: Identification of mantle cell lymphomas

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


Soybean IgG

Interpretation: mcg/mL of IgG Lower Limit of Quantitation* 2.0 Upper Limit of Quantitation** 200

Reference Values: < 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Soybean IgG4

Interpretation: mcg/mL of IgG4 Lower Limit of Quantitation 0.15 Upper Limit of Quantitation 30.0

Reference Values: <0.15 mcg/mL
The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicated immunologic sensitization to the food allergen in question.

**Soybean, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>


**Special Red Cell Antigen Typing**

**Clinical Information:** The presence or absence of a cellular antigen is an inherited trait. As a general rule, individuals will not make antibody directed against an antigen present on their own red blood cells.
Useful For: Additional proof of alloantibody specificity This test is not useful for the purpose of establishing paternity Determining possible antibody specificities in complex cases

Interpretation: Each antigen typed will be listed by name, followed by "pos or +" indicating that the antigen is present, or by "neg or -" indicating that the antigen is absent.

Reference Values: Reported as positive or negative


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Specific Gravity, Body Fluid

Clinical Information: Specific gravity (SG), the ratio of the mass of a solution compared to the mass of an equal volume of water, is an estimate of the concentration of substances dissolved in the solution. Assessing whether a body fluid specimen is exudative or transudative in nature is the initial step in determining the etiology of the fluid. Transudative fluids result from hemodynamic aberrations or oncotic changes and are associated with ultrafiltration of serum across membranes. Transudates most commonly occur in association with clinically apparent conditions such as heart failure and cirrhosis. Exudative fluids tend to develop as a consequence of inflammation or malignant disorders such as tuberculosis, pneumonia or cancer, in which capillary permeability is increased, allowing large-molecular-weight compounds to be released into the accumulating fluid. If the fluid is transudate, further diagnostic procedures are often not necessary, however the presence of an exudative fluid often triggers additional testing that may be invasive in nature. Determination of body fluid SG can aid in the distinction between transudative and an exudative fluid. SG in exudates is greater than in transudates. This same information can be obtained from the total protein using 3 g/dL as the cutoff.

Useful For: Used to determine concentration of body fluid, to help determine type of body fluid

Interpretation: Exudate fluid SG is >1.015 and transudate fluid SG is <1.015, this same information can be obtained from the total protein using 3 g/dL as the cutoff.

Reference Values: No established reference values


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Specific Gravity, Urine

Clinical Information: Specific gravity (SG), the ratio of the mass of a solution compared to the mass of an equal volume of water, is an estimate of the concentration of substances dissolved in the solution. Urine SG can be used to assess the kidney’s ability to concentrate or dilute urine. However, because protein, glucose, and contrast dye have molecular masses that are relatively large compared to other major components of urine (eg, sodium, chloride, potassium), they disproportionately affect SG. In these cases, urine osmolality is a better measure of urine concentration.

Useful For: As a partial assessment of the kidney’s ability to concentrate urine

Interpretation: Low specific gravity (SG) (1.001-1.003) may indicate the presence of diabetes insipidus, a disease caused by impaired functioning of antidiuretic hormone (ADH). Low SG also may occur in patients with glomerulonephritis, pyelonephritis, and other renal abnormalities. In these cases the kidney has lost its ability to concentrate due to tubular damage. High SG may occur in patients with adrenal insufficiency, hepatic disease, congestive heart failure, or in patients experiencing excessive water loss due to sweating, fever, vomiting, or diarrhea.

Reference Values: 1.002-1.030

Specimen Source Identification

Clinical Information: For various reasons, the patient origin for a particular specimen may be questioned. This is especially true for paraffin-embedded material: labeling accuracy may be questioned or tissue from other sources may be included by mistake. Confirmation of the patient origin may be critical to the clinical workup of that patient. Molecular methods are now available to extract DNA from various sources, including paraffin-embedded material, and to compare the molecular fingerprint (genotype) of one specimen source with another one. Matching genotypes on multiple specimens suggest that they are derived from the same patient, whereas differences in genotype suggest different patient sources.

Useful For: Determining specimen origin when the patient identity of a specimen is in question

Interpretation: An interpretive report will be provided.


SS1PO SpecStain Grp I, microorg, ProfOnly (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

SS3PO SpecStain Grp III, enzyme, ProfOnly (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

HCFPC SpecStain, frozen (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

SS2PC SpecStain, Grp II, other (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

SS2PO SpecStain, Grp II, other, Prof Only (Bill Only)

Reference Values:
This test is for billing purposes only.
This is not an orderable test.

SS3PC 113322
SpecStain, Grp III, enzyme (Bill Only)
Reference Values:
This test is for billing purposes only.
This is not an orderable test.

FSPNG 57678
Spinach IgG
Interpretation: mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200
Reference Values:
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

SPIN 86312
Spinach, IgE
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive

SMNCS 65574

Spinal Muscular Atrophy Carrier Screening by Deletion/Duplication Analysis

Clinical Information: Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by motor neuron degeneration leading to muscular atrophy with progressive paralysis. It is a genetically complex condition that is traditionally divided into 5 subtypes, depending on the age at which symptoms present and the motor milestones that are achieved. Presentation can range from in utero joint contractures and lack of fetal movement (type 0), to loss of ambulation in adolescence or adulthood (type IV). All patients with SMA develop symmetrical loss of muscle control, most commonly affecting proximal muscles. The American College of Medical Genetics (ACMG) and The American College of Obstetricians and Gynecologists (ACOG) currently recommend offering SMA carrier screening to all couples, regardless of race or ethnicity, before conception or early in pregnancy. The most common form of SMA is associated with the loss of Survival Motor Neuron (SMN) protein, which is encoded by 2 or more genes on chromosome 5. The majority of SMN protein is expressed by the SMN1 gene but a small portion of SMN is also contributed by the SMN2 gene. In fact, SMN1 produces more than 90% of SMN protein while SMN2 produces about less than 10% of residual SMN protein. This occurs because SMN2 differs from SMN1 by 5 nucleotide changes, 1 of which leads to alternative exon 7 splicing, and a reduction of SMN2 expression. Most individuals have 2 copies of SMN1, but individuals with as many as 5 copies of SMN1 have been observed. In addition, individuals may also have 0 to 5 copies of SMN2. SMA is most commonly caused by a homozygous deletion of exon 7 in SMN1. However, some patients with this disorder may be compound heterozygotes, with a deletion of 1 copy of SMN1 and a point mutation in the other allele. The severity of a patient's disease is associated with the number of copies of SMN2 that are present and 3 or more SMN2 copies are associated with a milder SMA phenotype. As the SMA test is a quantitative assay for the number of SMN1 exon 7 deletions, any result showing 2 SMN1 copies may in fact have two normal copies of SMN1 in cis (on the same chromosome) and a copy of SMN1 with the exon 7 deletion on the other chromosome (in trans). This is called the "2+0" carrier genotype. The frequency of the "2+0" carrier genotype differs by ancestry and the table below contains prior and adjusted risk for SMA carrier status when 2 or 3 SMN1 copies are detected. SMA carrier status risk based on more than 1 SMN1 copies.(1) Adjusted Risk Ethnicity Prior Risk 2 SMN1 Copies 3 SMN1 Copies Caucasian 1 in 35 1 in 632 1 in 3,500 Ashkenazi Jewish 1 in 41 1 in 350 1 in 4,000 Asian 1 in 53 1 in 628 1 in 5,000 African American 1 in 66 1 in 121 1 in 3,000 Hispanic 1 in 117 1 in 1,061 1 in 11,000

Useful For: General population carrier screening for spinal muscular atrophy (SMA) Carrier screening for reproductive partners of known SMA carriers Carrier screening for parents of a child with a known deletion of the survival motor neuron 1 gene (SMN1) or other family history of SMA

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.

Spinal Muscular Atrophy Diagnostic Assay by Deletion/Duplication Analysis

Clinical Information: Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by motor neuron degeneration leading to muscular atrophy with progressive paralysis. It is a genetically complex condition that is traditionally divided into 5 subtypes, depending on the age at which symptoms present and the motor milestones that are achieved. Presentation can range from in utero joint contractures and lack of fetal movement (type 0), to loss of ambulation in adolescence or adulthood (Type IV). All patients with SMA develop symmetrical loss of muscle control, most commonly affecting proximal muscles. The American College of Medical Genetics (ACMG) and The American Congress of Obstetricians and Gynecologists (ACOG) currently recommend offering SMA carrier screening to all couples, regardless of race or ethnicity, before conception or early in pregnancy. The most common form of SMA is associated with the loss of survival motor neuron (SMN) protein, which is encoded by 2 or more genes on chromosome 5. The majority of SMN protein is expressed by the SMN1 gene but a small portion of SMN is also contributed by the SMN2 gene. In fact, SMN1 produces more than 90% of SMN protein, while SMN2 produces less than 10% of residual SMN protein. This occurs because SMN2 differs from SMN1 by 5 nucleotide changes, 1 of which leads to alternative exon 7 splicing, and a reduction of SMN2 expression. Most individuals have 2 copies of SMN1, but individuals with as many as 5 copies of SMN1 have been observed. In addition, individuals may also have 0 to 5 copies of SMN2. SMA is most commonly caused by a homozygous deletion of exon 7 in SMN1. However, some patients with this disorder may be compound heterozygotes, with a deletion of 1 copy of SMN1 and a point mutation in the other allele. The severity of a patient's disease is associated with the number of copies of SMN2 that are present and 3 or more SMN2 copies are associated with a milder SMA phenotype. As the SMA test is a quantitative assay for the number of SMN1 exon 7 deletions, any result showing 2 or more SMN1 copies may, in fact, have 2 copies of SMN1 in cis (on the same chromosome) and another SMN1 with the exon 7 deletion on the other chromosome (in trans). This is called the "2+0" carrier genotype. The frequency of the "2+0" carrier genotype differs by ancestry and the table below contains prior and adjusted risk for SMA carrier status when 2 or 3 SMN1 copies are detected. SMA carrier status risk based on more than 1 SMN1 copies.(1) Ethnicity Prior Risk Adjusted Risk 2 SMN1 Copies 3 SMN1 Copies Caucasian 1 in 35 1 in 632 1 in 3,500 Ashkenazi Jewish 1 in 41 1 in 350 1 in 4,000 Asian 1 in 53 1 in 628 1 in 5,000 African American 1 in 66 1 in 121 1 in 3,000 Hispanic 1 in 117 1 in 1,061 1 in 11,000

Useful For: First-tier newborn screening for spinal muscular atrophy (SMA) Prenatal testing for SMA Diagnostic testing to confirm a suspected diagnosis of SMA

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.

**SPINK1 Gene, Full Gene Analysis**

**Clinical Information:** Mutations in several genes, including PRSS1, CFTR, CTRC, and SPINK1 have demonstrated genetic susceptibility to chronic pancreatitis. Disease susceptibility may be monogenic, as is the case with PRSS1, digenic, or multigenic, and multifactorial in which multiple genes and environmental factors play a role in disease expression. The most common monogenic cause of hereditary pancreatitis, in which a single gene mutation confers major risk susceptibility to chronic pancreatitis, is the presence of a mutation in the PRSS1 gene. Biallelic mutations in the SPINK1 gene have also been associated with increased susceptibility to chronic pancreatitis, especially in families without PRSS1 mutations. However, it is currently unknown if biallelic mutations alone are sufficient to cause chronic pancreatitis or if other risk factors are required for disease expression. Additionally, heterozygous SPINK1 mutations appear to modify disease severity when observed in combination with mutations in other genes. Unlike PRSS1 mutations, SPINK1 mutations have been associated with alcohol-induced and tropical pancreatitis. Genetic testing for all 4 pancreatitis susceptibility genes, including SPINK1, is available by ordering HPPAN / Hereditary Pancreatitis Panel.

**Useful For:** Identification of gene mutations contributing to pancreatitis in an individual or family.

**Interpretation:** All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics (AMCG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Spinobulbar Muscular Atrophy (Kennedy Disease), Molecular Analysis**

**Clinical Information:** X-linked spinal and bulbar muscular atrophy (spinobulbar muscular atrophy: SBMA; or Kennedy disease) is characterized by onset of progressive muscle weakness, atrophy, and fasciculations typically in the fourth or fifth decade of life. Affected patients also have signs of androgen insensitivity such as gynecomastia, reduced fertility, and testicular atrophy. The clinical severity and age at onset can be quite variable, even within families. Because this is an X-linked disease, males manifest this disorder and females are generally asymptomatic carriers. However, there have been reports of female carriers who exhibit symptoms such as muscle weakness and cramping. SBMA is caused by an expansion
of the CAG trinucleotide repeat in exon 1 of the human androgen receptor (AR) gene. This trinucleotide
repeat is polymorphic in the general population, with the number of repeats ranging from 11 to 34. The
number of repeats found in affected individuals can range from 38 to 62. There is no consensus as to the
clinical significance of alleles of 35 CAG repeats and literature suggests that alleles of 36 to 37 CAG
repeats may be associated with reduced penetrance. As with other trinucleotide repeat disorders,
anticipation is frequently observed and larger CAG expansions are associated with earlier onset and a
more rapid clinical progression.

**Useful For:** Molecular confirmation of clinically suspected cases of sporadic or familial spinobulbar
muscular atrophy (SBMA) Presymptomatic testing for individuals with a family history of SBMA and a
documented expansion in the androgen receptor (AR) gene

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
Normal alleles: 11-34 CAG repeats
Abnormal alleles: 36-62 CAG repeats

An interpretive report will be provided.

**Clinical References:** Pinsky L, Beitel LK, Trifiro MA: Spinobulbar Muscular Atrophy. In The

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**Sporotrichosis Antibody, Serum**

**Clinical Information:** Sporotrichosis is an endemic fungal infection caused by the dimorphic
fungus Sporothrix schenckii. Most cases of sporotrichosis have been reported from the subtropical and
tropical regions of the Americas, but a global distribution is likely. The organism is often isolated from
soil, plants, or plant products (wood), and occupational or recreational exposure to these materials is
often implicated in infected individuals. Infections due to S schenckii can be differentiated into several
distinct syndromes: - The cutaneous form of the disease is most common, often arising from sites of
minor skin trauma. The primary erythematous, papulonodular lesion may range from several
millimeters to 4 cm in size. Secondary lesions develop proximally along lymphatic channels. These
generally painless lesions usually do not involve lymph nodes, although lymphadenopathy may develop.
- Extracutaneous sporotrichosis can be manifested as osteoarticular involvement of a single joint. Major
joints of the extremities (ankle, knee, elbow, hand) are most often involved. The affected joint is
swollen and painful, with an attendant effusion. Systemic symptoms are minimal. - Pulmonary
sporotrichosis with cavitary lesions also has been described. - A multifocal extracutaneous syndrome has
been described, consisting of multijoint involvement, or widely scattered cutaneous lesions.
Constitutional symptoms (fever, weight loss) are often noted, and spread to bone and central nervous
system may occur. Underlying immune system suppression is often a contributing factor. Untreated
infection is ultimately fatal. (1)

**Useful For:** Aiding in the diagnosis of extracutaneous sporotrichosis

**Interpretation:** Extracutaneous infections, including disseminated and articular infections, produce
positive tests. The test should be positive in approximately 90% to 95% of all primary sporotrichosis
infections. Specimens from these patients may become positive by 2 weeks after infection and are not
expected to remain positive for more than 7 months after the original primary infection. Agglutination
titers of 1:8 and higher indicate presumptive evidence of sporotrichosis.Titers of 1:4 to 1:8 are
commonly seen in normal persons. Some cutaneous infections are associated with negative serologic
results.

**Reference Values:**
Negative
Reference values apply to all ages.

**Clinical References:** 1. Rex JH, Okhuysen PC: Sporothrix schenckii. In Principles and Practice of
**Sporothrix Antibody, Spinal Fluid**

**Clinical Information:** Sporotrichosis is an endemic fungal infection caused by the dimorphic fungus Sporothrix schenckii. Most cases of sporotrichosis have been reported from the subtropical and tropical regions of the Americas, but a global distribution is likely. The organism is often isolated from soil, plants, or plant products (wood), and occupational or recreational exposure to these materials is often implicated in infected individuals. Infections due to S schenckii can be differentiated into several distinct syndromes: -The cutaneous form of the disease is most common, often arising from sites of minor skin trauma. The primary erythematous papulonodular lesion may range from several millimeters to 4 cm in size. Secondary lesions develop proximally along lymphatic channels. These generally painless lesions usually do not involve lymph nodes, although lymphadenopathy may develop. -Extracutaneous sporotrichosis can be manifested as osteoarticular involvement of a single joint. Major joints of the extremities (ankle, knee, elbow, hand) are most often involved. The affected joint is swollen and painful, with an attendant effusion. Systemic symptoms are minimal. -Pulmonary sporotrichosis with cavitary lesions also has been described. -A multifocal extracutaneous syndrome has been described, consisting of multijoint involvement, or widely scattered cutaneous lesions. Constitutional symptoms (fever, weight loss) are often noted, and spread to bone and central nervous system may occur. Underlying immune system suppression is often a contributing factor. Untreated infection is ultimately fatal.(1)

**Useful For:** Aiding in the diagnosis of extracutaneous sporotrichosis

**Interpretation:** Any titer should be considered clinically significant; however, clinical correlation must be present. Extracutaneous infections, including disseminated and articular infections, produce positive tests.

**Reference Values:**
Negative
Reference values apply to all ages.

**Clinical References:**

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**Spotted Fever Group Antibody, IgG and IgM, Serum**

**Clinical Information:** Species of Rickettsia are small (0.3-0.5 mcm x 1-2 mcm) obligately intracellular bacteria (Proteobacteria). They have a gram-negative cell wall structure. Rickettsia are found in arthropod hosts for at least part of their life cycle. Rickettsial infections in the United States are caused by 2 major groups within the genus Rickettsia: spotted fever group and typhus fever group. The spotted fever group includes R rickettsii (Rocky Mountain spotted fever), R akari, R conorii (Boutonneuse fever), R australis (Queensland tick typhus), and R sibirica (North Asian tick typhus). The typhus fever group includes R typhi (murine typhus; endemic typhus) and R prowazekii (epidemic typhus). R rickettsiae is the most common rickettsial species encountered in the United States and is transmitted through a tick vector (Dermacentor species or, less commonly, Rhipicephalus sanguineus). Following a 2- to 14-day incubation period, patients most commonly present with fever, chills, and myalgia. A maculopapular rash typically appears 2 to 5 days after fever onset, though approximately 10% of patients will not develop a rash. Antibodies to the spotted fever group agents are detectable within 7 to 10 days after illness onset. Demonstration of either 1) seroconversion or 2) a 4-fold change in IgG-specific antibody titers in acute and convalescent serum samples is consistent with acute or ongoing disease.

**Useful For:** Aids in the diagnosis of spotted fever group rickettsial infections
Interpretation: This test detects reactivity to the group-specific rickettsia. For example, antibody reactivity to the Rickettsia rickettsii will also react with other organisms within the spotted fever group. IgG \( \geq 1:256 \): -Serum end point titers of \( \geq 1:256 \) are considered presumptive evidence of recent or current infection by organisms of appropriate rickettsial antigen group. \( <1:256 \) and \( \geq 1:64 \): -Single serum end point titers \( \geq 1:64 \) and \( <1:256 \) are suggestive of infection at an undetermined time and may indicate either past infection or early response to a recent rickettsial infection. -A 4-fold or greater increase in IgG titer between 2 serum specimens drawn 1 to 2 weeks apart and tested in parallel is considered presumptive evidence of a recent or current infection. -In patients infected with organisms within the rickettsial groups, IgG antibody is generally detectable within 1 to 2 weeks of onset of symptoms, peaking within 1 to 2 months and declining thereafter. Following prompt antimicrobial treatment, titers generally remain within detectable levels until 8 to 11 months. With relapse, prior immunization, or delayed antibiotic treatment, IgG levels may remain elevated for more than a year postonset. IgM \( \geq 1:64 \): -Titers \( \geq 1:64 \) are considered presumptive evidence of recent or current infection by organisms of appropriate rickettsial antigen group. \( <1:64 \): -Titers \( <1:64 \) suggest that the patient does not have an acute rickettsial infection. -IgM class antibody is transiently detected within 1 to 2 weeks of onset of symptoms, usually declining rapidly within 3 months following prompt antibiotic treatment. These levels will also be elevated for an extended period with relapse, prior immunization, or delayed antibiotic treatment.

Reference Values:
IgG: \( <1:64 \)
IgM: \( <1:64 \)
Reference values apply to all ages.

Clinical References:

Spruce, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies react with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L  Interpretation
0                  Negative
1  0.35-0.69       Equivocal
2  0.70-3.49       Positive
3  3.50-17.4       Positive
4  17.5-49.9       Strongly positive
5  50.0-99.9       Strongly positive
6  > or =100       Strongly positive

Reference values apply to all ages.


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**Squa** 82797

**Squamous Cell Carcinoma Antigen, Serum**

Reference Values:
0.0 - 2.2 ng/mL

SCC antigen levels alone should not be interpreted as evidence of the presence or absence of malignant disease. In patients with known or expected cancer, other tests and procedures must be considered for diagnosis and patient management. Results obtained with different assay methods or kits cannot be used interchangeably.

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**SQUA** 57312

**Squash, IgE**

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L  Interpretation
### Squid, IgE

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**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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**FSRP**

**SRP**

**Interpretation:** Signal Recognition Particle (SRP) is a myositis specific autoantibody which is seen in 5-10% of adult and juvenile myositis. Symptoms often are acute onset of severe polymyositis with frequent myalgias, severe weakness and very high creatine kinase levels. Some adults experience cardiac involvement and palpitations. There is a poor response to therapy.

**Reference Values:**

Negative

**SSAB**

**SS-A and SS-B Antibodies, IgG, Serum**

**Clinical Information:** SS-A/Ro, SS-B/La, RNP, and Sm are autoantigens commonly referred to as extractable nuclear antigens (ENAs). Antibodies to ENAs are common in patients with connective tissue diseases (systemic rheumatic diseases). SS-A/Ro is composed of protein antigens of 52kD and 60 kD combined with cytoplasmic RNA species. SS-A/Ro antibodies occur in patients with several different connective tissue diseases including Sjogren's syndrome, an autoimmune disease that involves primarily the salivary and lachrymal glands (up to 90% of cases); lupus erythematosus (LE) (40%-60% of cases); and rheumatoid arthritis. SS-A/Ro antibodies are associated with childhood LE, neonatal LE, and with congenital heart block in infants born to mothers with LE.(1,2) SS-A/Ro antibodies have also been reported to be associated with features of extraglandular inflammation in patients with LE including vasculitis, purpura, cytopenias, and adenopathy. SS-B/La is composed of a 48-kD protein combined with RNA species. SS-B/La antibodies are found primarily in patients with Sjogren's syndrome or LE, where they occur with frequencies of approximately 60% and 15%, respectively.(1,2) SS-B/La antibodies occur only infrequently in the absence of SS-A/Ro antibodies. See Connective Tissue Disease Cascade (CTDC) in Special Instructions and Optimized Laboratory Testing for Connective Tissue Diseases in Primary Care: The Mayo Connective Tissue Diseases Cascade in Publications.

**Useful For:** Evaluating patients with signs and symptoms of a connective tissue disease in whom the test for antinuclear antibodies is positive, especially those with signs and symptoms consistent with Sjogren's syndrome or lupus erythematosus

**Interpretation:** A positive result for SS-A/Ro or SS-B/La antibodies is consistent with connective tissue disease, including Sjogren's syndrome, lupus erythematosus (LE), or rheumatoid arthritis. A positive result for SS-A/Ro antibodies in a woman with LE prior to delivery indicates an increased risk of congenital heart block in the neonate.

**Reference Values:**

SS-A/Ro ANTIBODIES, IgG

<1.0 U (negative)

> or =1.0 U (positive)

Reference values apply to all ages.

SS-B/La ANTIBODIES, IgG

<1.0 U (negative)

> or =1.0 (positive)

Reference values apply to all ages.

SS-A/Ro Antibodies, IgG, Serum

**Clinical Information:** SS-A/Ro is an extractable nuclear antigen (ENA) composed of protein antigens of 52 kD and 60 kD combined with cytoplasmic RNA species. SS-A/Ro antibodies occur in patients with several different connective tissue diseases including Sjögren syndrome, an autoimmune disease that involves primarily the salivary and lachrymal glands (up to 90% of cases); lupus erythematosus (LE) (40%-60% of cases); and rheumatoid arthritis. SS-A/Ro antibodies are associated with childhood LE, neonatal LE, and with congenital heart block in infants born to mothers with LE. SS-A/Ro antibodies have also been reported to be associated with features of extraglandular inflammation in patients with LE including vasculitis, purpura, cytopenias, and adenopathy. SS-A/Ro is 1 of 4 autoantigens commonly referred to as extractable nuclear antigens (ENAs). The other ENAs are SS-B/La, RNP, and Sm. Each ENA is composed of 1 or more proteins associated with small nuclear or cytoplasmic RNA species (snRNP) ranging in size from 80 to 350 nucleotides. Antibodies to ENAs are common in patients with connective tissue diseases (systemic rheumatic diseases) including LE, mixed connective tissue disease, Sjögren syndrome, scleroderma (systemic sclerosis), and polymyositis/dermatomyositis. See Connective Tissue Disease Cascade (CTDC) in Special Instructions.

**Useful For:** Evaluating patients with signs and symptoms of a connective tissue disease in whom the test for antinuclear antibodies is positive

**Interpretation:** A positive result for SS-A/Ro antibodies is consistent with connective tissue disease, including Sjögren syndrome, lupus erythematosus (LE), or rheumatoid arthritis. A positive result for SS-A/Ro antibodies in a woman with LE prior to delivery indicates an increased risk of congenital heart block in the neonate.

**Reference Values:**
- <1.0 U (negative)
- ≥1.0 U (positive)

Reference values apply to all ages.

**Clinical References:**

SS-B/La Antibodies, IgG, Serum

**Clinical Information:** SS-B/La is an extractable nuclear antigen (ENA) composed of a 48-kD protein combined with RNA species. SS-B/La antibodies are found primarily in patients with Sjögren syndrome or lupus erythematosus (LE), where they occur with frequencies of approximately 60% and 15%, respectively. SS-B/La antibodies occur only infrequently in the absence of SS-A/Ro antibodies. SS-B/La is 1 of 4 autoantigens commonly referred to as extractable nuclear antigens (ENAs). The other ENAs are SS-A/Ro, RNP, and Sm. Each ENA is composed of 1 or more proteins associated with cytoplasmic or small nuclear RNA species (snRNP) ranging in size from 80 to 350 nucleotides. Antibodies to ENAs are common in patients with connective tissue diseases (systemic rheumatic diseases) including LE, mixed connective tissue disease, Sjögren syndrome, scleroderma (systemic sclerosis), and polymyositis/dermatomyositis. See Connective Tissue Disease Cascade (CTDC) in Special Instructions.

**Useful For:** Evaluating patients with signs and symptoms of a connective tissue disease in whom the test for antinuclear antibodies is positive

**Interpretation:** A positive result for SS-B/La antibodies is consistent with connective tissue disease, including Sjögren syndrome and lupus erythematosus.
St. Louis Encephalitis Antibody Panel, IgG and IgM, Spinal Fluid

Clinical Information: Since 1933, outbreaks of St. Louis encephalitis (SLE) have involved the western United States, Texas, the Ohio-Mississippi Valley, and Florida. The vector of transmission is the mosquito. Peak incidence occurs in summer and early autumn. Disease onset is characterized by generalized malaise, fever, chills, headache, drowsiness, nausea, and sore throat or cough followed in 1 to 4 days by meningeal and neurologic signs. The severity of illness increases with advancing age; persons over 60 years have the highest frequency of encephalitis. Symptoms of irritability, sleeplessness, depression, memory loss, and headaches can last up to 3 years. Infections with arboviruses, including SLE, can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age, sex, and occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age. SLE tends to produce the most severe clinical infections in older persons.

Useful For: Aiding the diagnosis of St. Louis encephalitis

Interpretation: Detection of organism-specific antibodies in the cerebrospinal fluid (CSF) may suggest central nervous system (CNS) infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of CNS infection.

Reference Values:
- IgG: <1:10
- IgM: <1:10

Reference values apply to all ages.

Clinical References:

St. Louis Encephalitis Antibody, IgG and IgM, Serum

Clinical Information: The onset of St. Louis encephalitis is characterized by generalized malaise, fever, chilliness, headache, drowsiness, nausea, and sore throat or cough followed in 1 to 4 days by the meningeal and neurologic signs. The severity of illness increases with advancing age; persons over 60 years have the highest frequency of encephalitis. Symptoms of irritability, sleeplessness, depression, memory loss, and headaches can last up to 3 years. Areas of outbreaks since 1933 have involved the western United States, Texas, the Ohio-Mississippi Valley, and Florida. The vector of transmission is the mosquito. Peak incidence of St. Louis encephalitis is associated with summer and early autumn.

Useful For: Aiding in the diagnosis of St. Louis encephalitis
Interpretation: In patients infected with the St. Louis encephalitis virus, IgG antibody is generally detectable within 1 to 3 weeks of onset, peaking within 1 to 2 months, and declining slowly thereafter. IgM class antibody is also reliably detected within 1 to 3 weeks of onset, peaking and rapidly declining within 3 months. A single serum specimen IgG of 1:10 or greater indicates exposure to the virus. Results from a single serum specimen can differentiate early (acute) infection from past infection with immunity if IgM is positive (suggests acute infection). While a 4-fold or greater rise in IgG antibody titer in acute and convalescent sera indicates recent infection. Infections with St. Louis encephalitis can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age and sex, as well as the occupational, vocational, and recreational habits of the individuals. St. Louis encephalitis tends to produce the most severe clinical infections in older persons.

Reference Values:
IgG: <1:10
IgM: <1:10

Reference values apply to all ages.

Clinical References:

ST2, Serum
Clinical Information: Heart failure is a chronic, progressive, complex cardiovascular disorder with a variety of etiologies and heterogeneity with respect to the clinical presentation of the patient. Heart failure is significantly increasing in prevalence with an aging population and is associated with high short- and long-term mortality rate. Over 80% of patients diagnosed and treated for acute heart failure syndromes in the emergency department are readmitted within the forthcoming year, incurring costly treatments and therapies.(1) The development and progression of heart failure is a clinically silent process until manifestation of the disorder, which typically occurs late and irreversibly into its progression. Mechanistically heart failure, whether due to systolic or diastolic dysfunction, is thought to progress primarily through adverse cardiac remodeling and fibrosis in response to cardiac injury or stress.(2) Soluble ST2 (sST2) is a biomarker that appears to be actively involved with IL-33 in modulating cardiac remodeling and ventricular function via effects in the inflammatory and apoptosis pathways.(3) ST2 is a member of the interleukin-1 receptor family and has 2 isoforms that are directly implicated in progression of cardiac disease: soluble ST2 (sST2) and a transmembrane-bound form, ST2 ligand (ST2L). IL-33 is the hormone that interacts with ST2L, protecting against left ventricular hypertrophy and myocardial fibrosis to effectively preserve cardiac function. Therefore, when sST2 concentrations are high, IL-33 is unavailable for cardioprotective signaling, leaving the heart vulnerable to the effects of sST2. High concentrations of sST2 result in cellular death, tissue fibrosis, reduced cardiac function, and an increase in the rate of disease progression.

Useful For: Aiding in prognosis for patients diagnosed with chronic heart failure

Interpretation: Clinically, ST2 concentrations in the HF-ACTION heart failure study were a significant predictor of mortality, all-cause hospitalization, mortality due to cardiovascular disease, and hospitalization due to cardiovascular disease using a cutoffpoint of 35 ng/mL. In addition, mortality risk was significantly higher in patients with ST2 >35 ng/mL.(4) The risk appears early and persists throughout the follow-up period. Clinical risk categories are substantiated by results from several large chronic heart failure studies: -Low risk: < or =35.0 ng/mL -High risk: >35.0 ng/mL (high risk) Results should be interpreted in the context of the individual patient presentation. Elevated ST2 results indicate an increased risk for adverse outcomes and signal the adverse remodeling and progression of disease. The reference interval was derived from normal donors without a history of cardiovascular disease, stroke, diabetes, renal disease, liver disease, or autoimmune diseases. The reference range is gender

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dependent; however, it is the clinical cutpoint that is recognized as providing the most utility. Knowledge of ST2 results in a heart failure patient may assist in cardiovascular risk stratification and lead to more aggressive management. There are no specific ST2 inhibitors available at this time and heart failure patients with elevated ST2 concentrations should be treated and monitored according to established guidelines. Angiotensin receptor blockers (ARBs) and aldosterone antagonists are thought to be particularly effective.

**Reference Values:**

**Males:**

- <24 months: not established
- 2-17 years: < or =43.0 ng/mL
- > or =18 years: < or = 52.0 ng/mL

**Females:**

- <24 months: not established
- 2-17 years: < or =43.0 ng/mL
- > or =18 years: < or =38.7 ng/mL

**Clinical References:**


**Stachybotrys chartarum/atra IgE**

**Interpretation:**

- Class IgE (kU/L)
- Comment 0 <0.10 Negative
- 0.10 – 0.34 Equivocal/Borderline
- 0.35 – 0.69 Low Positive
- 0.70 – 3.49 Moderate Positive
- 3.50 – 17.49 High Positive
- 17.50 – 49.99 Very High Positive
- >99.99 Very High Positive

**Reference Values:**

- <0.35 kU/L

**Stachybotrys Panel II**

**Reference Values:**

- Stachybotrys chartarum/atra IgE: <0.35 kU/L
- Stachybotrys chartarum/atra IgG: <20.4 mcg/mL
- Stachybotrys chartarum/atra IgA: <1.0 mg/L

**Stemphyllium, IgE**

**Clinical Information:**

Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for
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**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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**Sterols, Plasma**

**Clinical Information:** Cholesterol plays an essential role in many cellular and developmental processes. In addition to its role as a membrane lipid, it is the precursor to numerous molecules that play an important role in cell growth and differentiation, protein glycosylation, and signaling pathways. The biosynthesis of cholesterol and its subsequent conversion to other essential compounds is complex, involving a number of intermediates and enzymes. Disorders that result from a deficiency of these enzymes lead to an accumulation of specific intermediates and inhibit the formation of important biomolecules. Clinical findings common to cholesterol biosynthesis disorders include congenital skeletal malformations, dysmorphic facial features, psychomotor retardation, and failure to thrive. Desmosterolosis (desmosterol reductase deficiency) is a very rare disorder of cholesterol biosynthesis with a clinical phenotype similar to that of Smith-Lemli-Opitz (SLO) syndrome (7-dehydrocholesterol reductase deficiency). To date, less than 10 cases of desmosterolosis have been described. Its biochemical marker is the elevation of desmosterol in plasma, tissue, and cultured cells. Another very rare disorder of cholesterol biosynthesis is lathosterolosis caused by mutations in SC5DL (sterol 3-beta-hydroxysteroid-delta-5-desaturase). Less than 5 patients have been described to date, but the phenotype appears to be characterized by dysmorphic features, multiple congenital anomalies including those of limb and kidney, intellectual disability, and liver disease. Biochemical abnormalities include elevated lathosterol and transaminases, hyperbilirubinemia, and absent 7-dehydrocholesterol. Sitosterolemia is a rare autosomal recessive disorder caused by mutations in the ATP-binding cassette
(ABC) transporter genes, ABCG5 and ABCG8, which abnormally enhance the absorption of plant sterols and cholesterol from the intestines. Patients often present with hematologic abnormalities and tendon and tuberous xanthomas as well as premature coronary artery disease. A biochemical diagnosis of sitosterolemia is made by documenting elevations of the plant sterols sitosterol and campesterol in plasma or serum. Cerebrotendinous xanthomatosis (CTX), also known as 27-hydroxylase deficiency, is an autosomal recessive sterol storage disease causing accumulation of cholestanol and cholesterol in most tissues and markedly increased levels of cholestanol in serum. Clinical symptoms, which are variable, develop gradually and can include early chronic diarrhea, followed by bilateral cataracts, tuberous and tendon xanthomas, early atherosclerosis, and progressive neurologic impairment such as ataxia, paraparesis, cerebellar ataxia, and dementia. CTX should be suspected in patients with tendon xanthomas and normal or elevated serum cholesterol, and considered in cases of unexplained juvenile cataracts.

**Useful For:** Investigation of possible desmosterolosis (desmosterol reductase deficiency), cerebrotendinous xanthomatosis, lathosterolosis, and sitosterolemia

**Interpretation:** A quantitative report of the patient's sterol profile and a Biochemical Genetics consultant's interpretation is provided for each specimen.

**Reference Values:**

**DESMOSTEROL**
0.0-2.0 mg/L

**LATHOSTEROL**
0.0-3.0 mg/L

**CAMPESTEROL**
0.0-7.0 mg/L

**SITOSTEROL**
0.0-5.0 mg/L

**CHOLESTANOL**
0.0-5.0 mg/L

**Clinical References:**

**INSEC**

**Stinging Insects Allergen Profile**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and
clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children <5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens responsible for anaphylaxis, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**STK11 Gene, Full Gene Analysis**

**Clinical Information:** Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder characterized by gastrointestinal (GI) hamartomatous polyps and melanotic macules. The GI polyps are most common in the small intestine. Although typically benign, these polyps can cause chronic bleeding and may result in obstruction and intussusception. Pigment changes, typically dark blue spots around the lips, buccal mucosa, and fingers, appear in childhood. Affected individuals are also at an increased risk for a variety of malignancies including colorectal, gastric, breast, thyroid, pancreatic, uterine, and sertoli cell and sex cord tumors. PJS is caused by mutations in the STK11 (formerly LKB1) gene.

**Useful For:** Confirming a diagnosis of Peutz-Jeghers syndrome

**Interpretation:** All detected alterations will be evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.(1) Variants will be classified based on known, predicted, or possible pathogenicity, and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**

An interpretive report will be provided.

**FSTBG**

**Strawberry IgG**

**Interpretation:** mcg/mL of IgG

**Lower Limit of Quantitation:** 2.0

**Upper Limit of Quantitation:** 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**STBY**

**Strawberry, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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Streptococcal Antibodies Profile

Clinical Information: A number of bacterial antigens have been identified in cultures of group A streptococci. These extracellular products are primarily enzymatic proteins and include streptolysin O, streptokinase, hyaluronidase, deoxyribonucleases (DNases A, B, C, and D), and nicotinamide adenine nucleotidase. Infections by the group A streptococci are unique because they can be followed by the serious nonpurulent complications of rheumatic fever and glomerulonephritis. Recent information suggests that rheumatic fever is associated with infection by certain rheumatogenic serotypes (M1, M3, M5, M6, M18, and M19), while glomerulonephritis follows infection by nephritogenic serotypes (M2, M12, M49, M57, M59, and M60). Glomerulonephritis and rheumatic fever occur following the infection, after a period of latency following the infection, during which the patient is asymptomatic. The latency period for glomerulonephritis is approximately 10 days, and for rheumatic fever the latency period is 20 days.

Useful For: Demonstration of acute or recent streptococcal infection

Interpretation: Elevated values are consistent with an antecedent infection by group A streptococci. Although the antistreptolysin O (ASO) test is quite reliable, performing the anti-DNase is justified for 2 primary reasons. First, the ASO response is not universal. Elevated ASO titers are found in the sera of about 85% of individuals with rheumatic fever; ASO titers remain normal in about 15% of individuals with the disease. The same holds true for other streptococcal antibody tests: a significant portion of individuals with normal antibody titers for 1 test will have elevated antibody titers for another test. Thus, the percentage of false-negatives can be reduced by performing 2 or more antibody tests. Second, skin infections, in contrast to throat infections, are associated with a poor ASO response. Patients with acute glomerulonephritis following skin infection (post-impetigo) have an attenuated immune response to streptolysin O. For such patients, performance of an alternative streptococcal antibody test such as anti-DNase B is recommended.

Reference Values:
ANTISTREP-O TITER
5-17 years: < or =70 IU/mL
> or =18 years: < or =530 IU/mL

ANTI-DNase B TITER
<5 years: < or =250 U/mL
5-17 years: < or =375 U/mL
> or =18 years: < or =300 U/mL


Streptococcus pneumoniae Antigen, Spinal Fluid

Clinical Information: Streptococcus pneumoniae is the most frequently encountered bacterial agent of community-acquired pneumonia, and can also be an agent of bacterial meningitis. Because of
the significant morbidity and mortality associated with pneumococcal pneumonia, septicemia, and meningitis, it is important to have diagnostic test methods available that can provide a rapid diagnosis. In instances where empirical antibiotics are being considered prior to culture confirmation, antigen testing may be useful.

**Useful For:** Rapid diagnosis of pneumococcal meningitis

**Note:** According to the College of American Pathologists (CAP, IMM.41830), cerebrospinal fluid (CSF) samples collected to make an initial diagnosis and submitted for detection of Streptococcus pneumoniae antigen testing should also be submitted for routine bacterial culture. Mayo Medical Laboratories recommends that CSF bacterial cultures be performed at the originating site.

**Interpretation:** A positive result supports a diagnosis of pneumococcal meningitis. A negative result suggests that pneumococcal antigen is absent in the cerebrospinal fluid (CSF). However, infection due to Streptococcus pneumoniae cannot be ruled out since the antigen present in the specimen may be below the lower limit of detection of the test. If pneumococcal meningitis is suspected, bacterial culture and Gram-stain analysis on CSF should be performed.

**Reference Values:**

Negative

Reference values apply to all ages.

**Clinical References:**


**Streptococcus pneumoniae Antigen, Urine**

**Clinical Information:** Streptococcus pneumoniae is the most frequently encountered bacterial agent of community-acquired pneumonia (CAP). Because of the significant morbidity and mortality associated with pneumococcal pneumonia, septicemia, and meningitis, it is important to have diagnostic test methods available that can provide a rapid diagnosis. In instances where empirical antibiotics are provided for CAP without culture confirmation of Streptococcus pneumoniae, antigen testing may be useful.

**Useful For:** Rapid diagnosis of pneumococcal pneumonia

**Interpretation:** A positive result is indicative of pneumococcal pneumonia. A negative result is a presumptive negative for pneumococcal pneumonia, suggesting no current or recent pneumococcal infection. Infection due to Streptococcus pneumoniae cannot be ruled out since the antigen present in the specimen may be below the detection limit of the test. Pneumococcal pneumonia is best diagnosed by sputum culture.

**Reference Values:**

Negative

**Clinical References:**


**Streptococcus pneumoniae IgG Antibodies, 23 Serotypes, Serum**

**Clinical Information:** Streptococcus pneumoniae is a gram-positive bacteria that causes a variety of infectious diseases in children and adults, including invasive disease (bacteremia and meningitis) and infections of the respiratory tract (pneumonia and otitis media).(1,2) In 2009, it is estimated that Streptococcus pneumoniae was responsible for approximately 43,500 infections and 5,000 deaths in the United States. More than 90 serotypes of Streptococcus pneumoniae have been identified, based on
varying polysaccharides that are found in the bacterial cell wall. The serotypes responsible for disease vary with age and geographic location. Bacterial polysaccharides induce a T-cell independent type II humoral immune. Vaccines containing bacterial polysaccharides can be effective in generating an immune response that results in production of IgG antibodies and generation of long-lived plasma and memory B cells, which can protect an individual against bacterial disease. Active immunization of adults and children >2 years is performed with nonconjugated polysaccharide vaccines (Pneumovax and Pnu-Immune 23) that contain a total of 23 serotypes, namely 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F.(3) These 23 serotypes were included because, as a group, they account for approximately 90% of invasive pneumococcal infections. Antibody responses develop in approximately 75% to 85% of nonimmunocompromised adults and older children approximately 4 to 6 weeks following immunization. Immunization with a 23-valent vaccine is recommended for all adults > or =65 years of age and for adults 18 to 64 years of age with certain chronic diseases (heart disease, lung disease, type I diabetes, liver disease), those who are immunocompromised (congenital or acquired immunodeficiencies, malignancy, solid-organ transplant), and those with functional or anatomic asplenia.(3) In contrast to adults and older pediatrics, immune responses to polysaccharide antigens in children <2 years of age are generally weak. Active immunization of children <2 years requires multiple injections of vaccine prepared from purified polysaccharides conjugated to an immunogenic carrier (Corynebacterium diphtheria strain C7 protein), which results in a T-cell dependent antibody response. Prior to the availability of routine Streptococcus pneumoniae vaccination, in children <6 years, 7 serotypes (4, 6B, 9V, 18C, 19F, and 23F) accounted for 80% of invasive disease and up to 100% of all isolates that were found to be highly resistant to treatment with penicillin. The first conjugated vaccine available for children <2 years (Prevnar) contained these 7 serotypes.(4,5) The vaccine was highly effective, with invasive disease in children less than 5 years of age reduced from 99 to 21 cases per 100,000 population from 1998 to 2008. In addition, it was demonstrated that, after Prevnar became part of the routine vaccination schedule, only 2% of invasive disease was associated with any of the serotypes present in the 7-valent conjugate vaccine. Instead, approximately 61% of the invasive disease was caused by an additional 6 serotypes, including 1, 3, 5, 6A, 7F, and 19A. This led to development of a 13-valent Streptococcus pneumoniae polysaccharide conjugate vaccine, which is marketed as Prevnar13. Prevnar13 is approved for administration to all children ages 6 weeks to 71 months, and has replaced the previous 7-valent Prevnar vaccine.(6) Patients with intrinsic defects in humoral immunity, such as common variable immunodeficiency, may have impaired antibody responses to pneumococcal vaccination. Further, impaired polysaccharide responsiveness, also known as selective antibody deficiency, is a recognized clinical entity in patients >2 years and is characterized by recurrent bacterial respiratory infections, absent or subnormal antibody response to a majority of the polysaccharide antigens, and normal or increased immunoglobulin levels, including IgG subclasses, in the context of an intact humoral response to protein antigens. In several other primary immunodeficiencies, including Wiskott-Aldrich syndrome, autoimmune lymphoproliferative syndrome, and DiGeorge syndrome, IgG subclass deficiencies may also result in impaired antibody responses to polysaccharide antigens.

**Useful For:** Assessing the IgG antibody response to active immunization with nonconjugated, 23-valent vaccines Assessing the IgG antibody response to active immunization with conjugated, 13-valent vaccines Determining the ability of an individual to produce an antibody response to polysaccharide antigen(s), as part of an evaluation for humoral or combined immunodeficiencies

**Interpretation:** As a general guideline, nonimmunocompromised adults develop IgG antibodies approximately 4 to 6 weeks following nonconjugated vaccination. A study conducted at the Mayo Clinic assessed IgG antibody concentrations prior to and following vaccination in a cohort of 100 healthy adults who met stringent exclusion criteria, including lack of previous pneumococcal vaccination or pneumonia associated with Streptococcus pneumoniae infection. Based on this data, reference ranges were established that most effectively discriminated between prevaccination and postvaccination antibody concentrations. Antibody concentrations greater than or equal to the reference value for at least 50% of serotypes in either a pre- or postvaccination specimen or a 2-fold or greater increase in antibody concentrations for at least 50% of serotypes when comparing the pre- to the postvaccination results would be consistent with a normal response to Streptococcus pneumoniae vaccination. Serotype-specific antibodies may persist for up to 10 years following immunization or infection.

**Reference Values:**
<table>
<thead>
<tr>
<th>Serotype</th>
<th>Normal Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (1)</td>
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</tr>
<tr>
<td>2 (2)</td>
<td>&gt; or =1.0</td>
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<td>4 (4)</td>
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<tr>
<td>5 (5)</td>
<td>&gt; or =10.7</td>
</tr>
<tr>
<td>8 (8)</td>
<td>&gt; or =2.9</td>
</tr>
<tr>
<td>9N (9)</td>
<td>&gt; or =9.2</td>
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<tr>
<td>12F (12)</td>
<td>&gt; or =0.6</td>
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<td>14 (14)</td>
<td>&gt; or =7.0</td>
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<td>17F (17)</td>
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<tr>
<td>19F (19)</td>
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<tr>
<td>20 (20)</td>
<td>&gt; or =1.3</td>
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<td>23F (23)</td>
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<td>6B (26)</td>
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<td>11A (43)</td>
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<td>19F (57)</td>
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<tr>
<td>9V (68)</td>
<td>&gt; or =2.6</td>
</tr>
<tr>
<td>33F (70)</td>
<td>&gt; or =1.7</td>
</tr>
</tbody>
</table>

**Clinical References:**
**Striational (Striated Muscle) Antibodies, Serum**

**Clinical Information:** Autoantibodies directed against the contractile elements of striated muscle are found in 30% of adult patients with myasthenia gravis and in 80% of those with thymoma. These antibodies may also be detected in patients with: Lambert-Eaton myasthenic syndrome, small-cell lung carcinoma, breast carcinoma, patients treated with D-penicillamine, bone marrow transplant recipients having graft-versus-host disease, and autoimmune liver disorders. While this test is used as a serological aid in the diagnosis of thymoma, especially in patients with onset of myasthenia gravis (MG) younger than 45 years, it is more predictive of thymoma when accompanied by a muscle acetylcholine receptor (AChR) modulating antibody value of 90% or greater AChR loss and is most predictive of thymoma when accompanied by collapsin response-mediator protein-5-IgG (CRMP-5-IgG). Serial measurements are useful after treatment of thymoma. Measurements of muscle AChR binding, muscle AChR modulating antibody, and CRMP-5-IgG (if initially positive) are also recommended.

**Useful For:** As a serological aid in the diagnosis of thymoma, especially in patients with onset of myasthenia gravis (MG) younger than 45 years. As a screening test for MG in older patients, especially when tests for muscle acetylcholine receptor (AChR) antibodies are negative. Serial measurements are useful in monitoring the efficacy of immunosuppressant treatment in patients with MG. Serial measurements are useful after treatment of thymoma. Serial measurements in recipients of D-penicillamine or bone marrow allografts may be useful in monitoring autoimmune complications and graft-versus-host disease, respectively.

**Interpretation:** Striational antibodies occur in approximately: -14% of patients with thymoma without clinical evidence of myasthenia gravis (MG) -30% of patients with acquired (autoimmune) MG -74% of patients with thymoma in association with MG -25% of rheumatoid arthritis (RA) patients treated with D-penicillamine, 4% in untreated RA patients -5% of patients with Lambert-Eaton myasthenic syndrome (LES) and/or small-cell lung carcinoma (SCLC) (MGL1 / Myasthenia Gravis [MG]/Lambert-Eaton Syndrome [LES] Evaluation and PAVAL / Paraneoplastic Autoantibody Evaluation, Serum) -In some bone marrow recipients with graft-versus-host disease The incidence in healthy subjects is under 1%. A rising titer after removal of thymoma may be indicative of tumor recurrence.

**Reference Values:**

<1:120

**Clinical References:**

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**Strict Criteria Sperm Morphology for Infertility Diagnosis and Treatment, Semen**

**Clinical Information:** Infertility affects 1 out of 6 couples of child-bearing age. Approximately 40% of infertility has a female-factor cause and 40% a male-factor cause. The remaining 20% of infertility is due to a combination of male- and female-factor disorders or is unexplained. Abnormalities in sperm morphology are related to: defects in sperm transport, sperm capacitation, the acrosome reaction, binding/penetration of the zona pellucida, and fusion with the oocyte vitelline membrane. All of these steps are essential to normal fertility. Strict criteria sperm morphology testing also greatly assists with selecting the most cost-effective in vitro sperm processing and insemination treatment for the couple's IVF cycle. Sperm with severe head abnormalities are unlikely to bind to the zona pellucida. These patients may require intracytoplasmic sperm injection in association with their IVF cycle to ensure optimal levels of fertilization are achieved. This, in turn, provides the patient with the best chance of pregnancy. Multiple semen analyses are usually conducted over the course of the spermatogenic cycle (approximately 70 days).
**Useful For:** Diagnosing male infertility Selecting the most cost-effective therapy for treating male-factor infertility Quantifying the number of germinal and WBCs per mL of semen

**Interpretation:** Categorizing sperm according to strict criteria based on measurements of head and tail sizes and shapes. Sperm with abnormalities in head/tail size/shape may not be capable of completing critical steps in sperm transport and fertilization.

**Reference Values:**
Normal forms
- > or = 4.0%
- Germinal cells/mL
  - < 4 x 10^6 (normal)
  - > or = 4 x 10^6 (Elevated germinal cells in semen are of unknown clinical significance)
- WBC/mL
  - < 1 x 10^6 (normal)
  - > or = 1 x 10^6 (Elevated white blood cells in semen are of questionable clinical significance)


**MSTC1 35184**

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**Useful For:** Diagnosing male infertility Selecting the most cost-effective therapy for treating male-factor infertility Quantifying the number of germinal and WBCs per mL of semen

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Normal forms: > or = 4.0%
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  - < 4 x 10^6 (normal)
  - > or = 4 x 10^6 (elevated germinal cells in semen are of unknown clinical significance)
- WBC/mL
  - < 1 x 10^6 (normal)
  - > or = 1 x 10^6 (elevated white blood cells in semen are of questionable clinical significance)

**Clinical References:** Kruger Morphology Conference, Boston, MA, October 9, 1993

**STRNG 63866**

**Strongyloides Antibody, IgG, Serum**

**Clinical Information:** Strongyloidiasis is caused by Strongyloides stercoralis, a nematode endemic to...
tropical and subtropical regions worldwide. *S. stercoralis* is also prominent in the southeastern United States, including in rural areas of Kentucky, Tennessee, Virginia, and North Carolina. A small series of epidemiological studies in the United States identified that between 0 to 6.1% of individuals sampled had antibodies to *S. stercoralis*. *S. stercoralis* has a complex lifecycle that begins with maturation to the infective filariform larva in warm, moist soil. The larvae subsequently penetrate exposed skin and migrate hematogenously to the lungs, from where they ascend the bronchial tree and are swallowed. Once in the small intestine, filariform larva mature into the adult worms that burrow into the mucosa. Gravid female worms produce eggs that develop into noninfectious rhabditiform larvae in the gastrointestinal tract and are eventually released in the stool. The time from dermal penetration to appearance of Strongyloides in stool samples is approximately 3 to 4 weeks. The most common manifestations of infection are mild and may include epigastric pain, mild diarrhea, nausea, and vomiting. At the site of filariform penetration, skin may be inflamed and itchy-this is referred to as “ground itch.” Migration of the larva through the lungs and up the trachea can produce a dry cough, wheezing, and mild hemoptysis. Eosinophilia, though common among patients with strongyloidiasis, is not a universal finding and the absence of eosinophilia cannot be used to rule-out infection. In some patients, particularly those with a depressed immune system, the rhabditiform larvae may mature into the infectious filariform larva in the gastrointestinal tract and lead to autoinfection. The filariform larvae subsequently penetrate the gastrointestinal mucosa, migrate to the lungs and can complete their lifecycle. Low-level autoinfection can maintain the nematode in the host for years to decades. Among patients who become severely immunocompromised, however, autoinfection may lead to hyperinfection and fatal disseminated disease. Hyperinfection has also been associated with underlying human T-cell lymphotropic virus type 1 (HTLV-1) infection. Uncontrolled, the larvae can disseminate to the lungs, heart, liver, and central nervous system. Septicemia and meningitis are common in cases of Strongyloides hyperinfection due to seeding of the bloodstream and central nervous system with bacteria originating from the gastrointestinal tract.

**Useful For:** Screening for the presence of IgG-class antibodies to Strongyloides
Not useful for monitoring patient response to therapy as IgG-class antibodies to Strongyloides may remain detectable following resolution of infection.

**Interpretation:** Positive: IgG antibodies to Strongyloides were detected, suggesting current or past infection. False-positive results may occur with other helminth infections (eg, Trichinella, Taenia solium). Clinical correlation is required. Negative: No detectable levels of IgG antibodies to Strongyloides. Repeat testing in 10 to 14 days if clinically indicated.

**Reference Values:**
Negative
Reference values apply to all ages.

**Clinical References:**

**STCH**

**Reference Values:**
Reporting limit determined each analysis

Potentially lethal concentrations are in excess of 500 ng/mL.
**Reference Values:**
Normal (Unexposed population):
  None detected

Exposed:
Biological Exposure Index (BEI):
  0.55 mg/L (end of shift)
  0.02 mg/L (prior to next shift)

Toxic:
  Not established

**SUAC**

**Succinylacetone, Blood Spot**

**Clinical Information:** Tyrosinemia type 1 (Tyr 1) is an autosomal recessive condition caused by fumarylacetoacetate hydrolase (FAH) deficiency. Tyr 1 can cause severe liver disease, hypophosphatemic rickets, renal tubular dysfunction, and neurologic crises. If left untreated, most patients die of liver failure in the first years of life. Treatment with 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3 cyclohexanediione is available and is particularly effective when initiated in newborns. The incidence of Tyr 1 is approximately 1 in 100,000 live births. While tyrosine can be determined by routine newborn screening, it is not a specific marker for Tyr I and often may be associated with common and benign transient tyrosinemia of the newborn. Succinylacetone (SUAC) is a specific marker for Tyr I, but is not detectable by routine newborn screening. This assay determines SUAC in newborn blood spots by tandem mass spectrometry. Additional follow-up testing may include confirmatory molecular analysis of the FAH gene.

**Useful For:** Second-tier newborn screening for tyrosinemia type 1 (Tyr 1) in blood spots with nonspecific elevations of tyrosine Diagnosis of Tyr 1 Follow-up of patients with Tyr 1

**Interpretation:** Normal: <5.0 mcM Elevations of succinylacetone (SUAC) above the reference range are indicative of tyrosinemia type 1 (Tyr 1). Patients with Tyr I who are treated with diet and/or 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3 cyclohexanediione (nitisinone) should have declining or normal values of SUAC.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FSUCC**

**Succinyladenosine, CSF**

**Reference Values:**
Reference Range: 0.74 â€“ 4.92 umol/L

**FSCNE**

**Sugar Cane (Saccharum officinarum) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive
Reference Values:
<0.35 kU/L

Sugarbeet Seed, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


Sugarbeet Weed, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of
sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>0</td>
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<td>4</td>
<td>17.5-49.9</td>
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<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


---

**Sulfamethoxazole, Serum**

**Clinical Information:** Sulfamethoxazole is a sulfonamide antibiotic that is administered in conjunction with another antibacterial, trimethoprim. These agents are used to treat a variety of infections including methicillin-resistant Staphylococcus aureus, and for prophylaxis in immunosuppressed patients such as HIV-positive individuals. Therapeutic drug monitoring is not commonly performed unless there are concerns about adequate absorption, clearance, or compliance. Monitoring of sulfamethoxazole is indicated only when prolonged (>3 months) therapy is required. Sulfamethoxazole is absorbed readily after oral administration, with peak serum concentration occurring 2 to 3 hours after an oral dose. Its average elimination half-life is 6 to 10 hours. Toxicity includes crystalluria with resultant calculi and renal disease. Toxicity is due to a high concentration of acetylated, relatively insoluble forms of the drug. Excess fluid should be taken with sulfamethoxazole to avoid formation of urine sulfonamide crystals.

**Useful For:** Monitoring therapy to ensure drug absorption, clearance, or compliance

**Interpretation:** Serum drug concentrations should be interpreted with respect to the minimum inhibitory concentration (MIC) of targeted organisms. Most patients will display peak steady-state serum concentrations >50 mcg/mL when drawn at least 1 hour after an oral dose. Targets concentrations may be higher, depending on the intent of therapy. For Pneumocystis carinii pneumonia (PCP pneumonia), peak concentrations: 100-150 mcg/mL Toxicity: >200 mcg/mL Toxicity (formation of urinary crystals) associated with sulfamethoxazole occurs with prolonged exposure to serum concentrations >125 mcg/mL.

**Reference Values:**

**SULFU 81815**

**Sulfate, 24 Hour, Urine**

**Clinical Information:** Urinary sulfate is a reflection of dietary protein intake, particularly meat, fish, and poultry, which are rich in sulfur-containing amino acids methionine and cysteine. Urinary sulfate can be used to assess dietary protein intake for nutritional purposes. A protein-rich diet has been associated with an increased risk for stone formation, possibly due, in part, to an increase in urinary calcium excretion caused by acid production from metabolism of sulfur-containing amino acids. Indeed, urinary sulfate excretion is higher in patients who have kidney stones than in individuals who do not form stones. Thus, urinary sulfate excretion may provide an index for protein-induced calciuria. Sulfate is a major anion in the urine that has significant affinity for cations and modulates the availability of cations for reacting with other anions in the urine. It thus is an important factor of urinary supersaturation for various crystals or stones such as calcium oxalate, hydroxyapatite, and brushite. For example, a high sulfate concentration may modulate the availability of calcium for reacting with oxalate and thus affect the propensity for calcium oxalate stone or crystal formation. Urinary sulfate also has a major impact on buffering or providing hydrogen ions and as such modulates the supersaturation of uric acid.

**Useful For:** Assessing the nutrition intake of animal protein The calculation of urinary supersaturation of various crystals or stones

**Interpretation:** Urinary sulfate is a reflection of dietary protein intake, particularly of meat, and thus can be used as an index of nutritional protein intake. It also is used in the calculation of urinary supersaturation of various crystals or stones.

**Reference Values:**
7-47 mmol/24 hours


**FSUAB 75230**

**Sulfatide Autoantibody Test**

**Clinical Information:** Background information: Peripheral neuropathies (PNs) are a group of neurological disorders affecting one or more of the peripheral nerves (1,2). Causes of PN include nerve compression, genetic mutations, inflammation, metabolic abnormalities, vitamin deficiencies, exposure to toxins or drugs, or the presence of autoimmune antibodies (1). Symptoms of PN vary based on location and mechanism of nerve damage but can include sensory impairment, distal weakness, loss of sensation, muscle weakness, and pain (1,2). PNs are typically classified based on the types of nerves

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affected, predominantly motor, predominantly sensory, or a combination of both (2). IgG and more commonly IgM Antibodies to sulfatide have been associated with sensory and sensory-motor neuropathies sometimes accompanied by pain (3,4,5). Additionally, IgG anti-sulfatide antibodies have been associated with distal sensory polyneuropathy (DSP) in individuals with HIV (6).

**Reference Values:**
A final report will be attached in MayoAccess.

**Clinical References:**

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**FSLFU**

**Sulfonylurea Screen, Urine**

**Reference Values:**
Reference Range: Not Established

<table>
<thead>
<tr>
<th>Drug</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetohepamide, UR</td>
<td>ug/mL</td>
</tr>
<tr>
<td>Chlorpropamide, UR</td>
<td>ug/mL</td>
</tr>
<tr>
<td>Tolazamide, UR</td>
<td>ug/mL</td>
</tr>
<tr>
<td>Tolbutamide, UR</td>
<td>ug/mL</td>
</tr>
<tr>
<td>Glimipide, UR</td>
<td>ng/mL</td>
</tr>
<tr>
<td>Glipizide, UR</td>
<td>ng/mL</td>
</tr>
<tr>
<td>Glyburide, UR</td>
<td>ng/mL</td>
</tr>
<tr>
<td>Nateglinide, UR</td>
<td>ng/mL</td>
</tr>
<tr>
<td>Repaglinide, UR</td>
<td>ng/mL</td>
</tr>
</tbody>
</table>

**FSUNG**

**Sunflower Seed IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**SUNFS**

**Sunflower Seed, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat
proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


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**Sunflower, IgE**

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Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.


SAT24
36971 Supersaturation Profile, 24 Hour, Urine

Clinical Information: Urine is often supersaturated, which favors precipitation of several crystalline phases such as calcium oxalate, calcium phosphate, and uric acid. However, crystals do not always form in supersaturated urine because supersaturation is balanced by crystallization inhibitors that are also present in urine. Urinary inhibitors include ions (eg, citrate) and macromolecules but remain poorly understood. Urine supersaturation is calculated by measuring the concentration of all the ions that can interact (potassium, calcium, phosphorus, oxalate, uric acid, citrate, magnesium, sodium, chloride, sulfate, and pH). Once the concentrations of all the relevant urinary ions are known, a computer program can calculate the theoretical supersaturation with respect to the important crystalline phases (eg, calcium oxalate).(1) Since the supersaturation of urine has been shown to correlate with stone type,(2) therapy is often targeted towards decreasing those urinary supersaturations that are identified. Treatment strategies include alterations in diet and fluid intake as well as drug therapy, all designed to decrease the urine supersaturation.

Useful For: Diagnosis and management of patients with renal lithiasis: -In patients who have a radiopaque stone, for whom stone analysis is not available, the supersaturation data can be used to predict the likely composition of the stone. This may help in designing a treatment program -Individual components of the supersaturation profile can identify specific risk factors for stones -During follow-up, changes in the urine supersaturation can be used to monitor the effectiveness of therapy by confirming that the crystallization potential has indeed decreased -Urine ammonium can be used to evaluate renal excretion of acid and urine pH -The protein catabolic rate, calculated from the urine urea nitrogen, can be used to estimate a patient's protein intake

Interpretation: Delta G (DG), the Gibbs free energy of transfer from a supersaturated to a saturated solution is negative for undersaturated solutions and positive for supersaturated solutions. In most cases the supersaturation levels are slightly positive even in normal individuals but are balanced by an inhibitor activity. While the DG of urine is often positive, even in the urine of nonstone formers, on average, the DG is even more positive in those individuals who do form kidney stones. The "normal" values were simply derived by comparing urinary DG values for the important stone-forming crystalline phases between a population of stone formers and a population of non-stone formers. Those DG values that are outside the expected range in a population of non-stone formers are marked "abnormal." If the urine citrate is low, secondary causes should be excluded including hypokalemia, renal tubular acidosis, gastrointestinal bicarbonate losses (eg, diarrhea or malabsorption), or an exogenous acid load (eg, excessive consumption of meat protein). A normal or increased citrate value suggests that potassium citrate may be a less effective choice for treatment of a patient with calcium oxalate or calcium phosphate stones. An increased urinary oxalate value may prompt a search for genetic abnormalities of oxalate production (ie, primary hyperoxaluria). Secondary hyperoxaluria can result from diverse gastrointestinal
disorders that result in malabsorption. Milder hyperoxaluria could result from excess dietary oxalate consumption, or reduced calcium (dairy) intake, perhaps even in the absence of gastrointestinal disease. High urine ammonium and low urinary pH suggests ongoing gastrointestinal losses. Such patients are at risk of uric acid and calcium oxalate stones. Low urine ammonium and high urine pH suggests renal tubular acidosis. Such patients are at risk of calcium phosphate stones. Patients with calcium oxalate and calcium phosphate stones are often treated with citrate to raise the urine citrate (a natural inhibitor of calcium oxalate and calcium phosphate crystal growth). However, since citrate is metabolized to bicarbonate (a base) this drug can also increase the urine pH. If the urine pH gets too high with citrate treatment, one may unintentionally increase the risk of calcium phosphate stones. Monitoring the urine ammonium is one way to titrate the citrate dose and avoid this problem. A good starting citrate dose is about one-half of the urine ammonium excretion (in mEq of each). One can monitor the effect of this dose on urine ammonium, citrate, and pH values, and adjust the citrate dose based upon the response. A fall in urine ammonium should indicate whether the current citrate is enough to partially (but not completely) counteract the daily acid load of that given patient. The protein catabolic rate is calculated from urine urea. Under routine conditions, the required protein intake is often estimated as 0.8 g/kg body weight. The results can be used to determine the likely effect of a therapeutic intervention on stone-forming risk. For example, taking oral potassium citrate will raise the urinary citrate excretion, which should reduce calcium phosphate supersaturation (by reducing free ionic calcium), but citrate administration also increases urinary pH (because it represents an alkali load) and a higher urine pH promotes calcium phosphate crystallization. The net result of this or any therapeutic manipulation could be assessed by collecting a 24-hour urine and comparing the supersaturation calculation for calcium phosphate before and after therapy. Important stone-specific factors: -Calcium oxalate stones: urine volume, calcium, oxalate, citrate, and uric acid excretion are all risk factors that are possible targets for therapeutic intervention. -Calcium phosphate stones (apatite or brushite): urinary volume, calcium, pH, and citrate significantly influence the supersaturation for calcium phosphate. Of note, a urine pH of less than 6 may help reduce the tendency for these stones to form. -Uric acid stones: urine pH, volume, and uric acid excretion levels influence the supersaturation. Urine pH is especially critical, in that uric acid is unlikely to crystallize if the pH is greater than 6. -Sodium urate stones: alkaline pH and high uric acid excretion promote stone formation. A low urine volume is a universal risk factor for all types of kidney stones.

Reference Values:

SUPERSATURATION REFERENCE MEANS (Delta G: DG)

Calcium oxalate: 1.77 DG
Brushite: 0.21 DG
Hydroxyapatite: 3.96 DG
Uric acid: 1.04 DG
Sodium urate: 1.76 DG

INDIVIDUAL URINE ANALYTES

OSMOLALITY

0-11 months: 50-750 mOsm/kg
> or =12 months: 150-1,150 mOsm/kg

pH

4.5-8.0

ALL REFERENCE RANGES BELOW ARE BASED ON 24-HOUR COLLECTIONS.

SODIUM

41-227 mmol/24 hours
Reference values have not been established for patients <16 years of age.

POTASSIUM

17-77 mmol/24 hours
Reference values have not been established for patients <16 years of age.

CALCIUM

Males: <250 mg/24 hours
Females: <200 mg/24 hours
Reference values have not been established for patients <18 years and >83 years of age

MAGNESIUM
51-269 mg/24 hours
Reference values have not been established for patients <18 years and >83 years of age

CHLORIDE
40-224 mmol/24 hours
Reference values have not been established for patients <16 years of age.

PHOSPHORUS
<1,100 mg/24 hours

SULFATE
7-47 mmol/24 hours

CITRATE EXCRETION
0-19 years: not established
20 years: 150-1,191 mg/24 hours
21 years: 157-1,191 mg/24 hours
22 years: 164-1,191 mg/24 hours
23 years: 171-1,191 mg/24 hours
24 years: 178-1,191 mg/24 hours
25 years: 186-1,191 mg/24 hours
26 years: 193-1,191 mg/24 hours
27 years: 200-1,191 mg/24 hours
28 years: 207-1,191 mg/24 hours
29 years: 214-1,191 mg/24 hours
30 years: 221-1,191 mg/24 hours
31 years: 228-1,191 mg/24 hours
32 years: 235-1,191 mg/24 hours
33 years: 242-1,191 mg/24 hours
34 years: 250-1,191 mg/24 hours
35 years: 257-1,191 mg/24 hours
36 years: 264-1,191 mg/24 hours
37 years: 271-1,191 mg/24 hours
38 years: 278-1,191 mg/24 hours
39 years: 285-1,191 mg/24 hours
40 years: 292-1,191 mg/24 hours
41 years: 299-1,191 mg/24 hours
42 years: 306-1,191 mg/24 hours
43 years: 314-1,191 mg/24 hours
44 years: 321-1,191 mg/24 hours
45 years: 328-1,191 mg/24 hours
46 years: 335-1,191 mg/24 hours
47 years: 342-1,191 mg/24 hours
48 years: 349-1,191 mg/24 hours
49 years: 356-1,191 mg/24 hours
50 years: 363-1,191 mg/24 hours
51 years: 370-1,191 mg/24 hours
52 years: 378-1,191 mg/24 hours
53 years: 385-1,191 mg/24 hours
54 years: 392-1,191 mg/24 hours
55 years: 399-1,191 mg/24 hours
56 years: 406-1,191 mg/24 hours
57 years: 413-1,191 mg/24 hours
58 years: 420-1,191 mg/24 hours
59 years: 427-1,191 mg/24 hours
60 years: 434-1,191 mg/24 hours
>60 years: not established

**OXALATE**
0.11-0.46 mmol/24 hours

**URIC ACID**
Diet-dependent: <750 mg/24 hours

**CREATININE**
Normal values mg per 24 hours:
Males: 955-2936 mg/24 hours
Females: 601-1689 mg/24 hours
Reference ranges for male and female patients <18 and >83 years of age have not been established.

The expected urine creatinine excretion per 24 hours:
Males: 13-29 mg/kg of body weight/24 hours
Females: 9-26 mg/kg of body weight/24 hours
Reference ranges for male and female patients <18 and >83 years of age have not been established.

Note: To convert to mg/kg of body weight/24 hours, divide the mg/24 hours result by body weight in kg.

**AMMONIUM**
15-56 mmol/24 hour
Reference values have not been established for patients <18 years and >77 years of age.

**UREA NITROGEN**
5.0-16.0 g/24 hours

**PROTEIN CATABOLIC RATE**
56-125 g/24 hours

**Clinical References:**

**Supersaturation Profile, Pediatric, Random, Urine**

**Clinical Information:** Urine is often supersaturated, which favors precipitation of several crystalline phases such as calcium oxalate, calcium phosphate, and uric acid. However, crystals do not always form in supersaturated urine because supersaturation is balanced by crystallization inhibitors that are also present in urine. Urinary inhibitors include ions (eg, citrate) and macromolecules but remain poorly understood. Urine supersaturation is calculated by measuring the concentration of all the ions that can interact (potassium, calcium, phosphorus, oxalate, uric acid, citrate, magnesium, sodium, chloride, sulfate, and pH). Once the concentrations of all the relevant urinary ions are known, a computer program can calculate the theoretical supersaturation with respect to the important crystalline phases (eg, calcium oxalate).(1) Since the supersaturation of urine has been shown to correlate with stone type,(2) therapy is often targeted towards decreasing those urinary supersaturations that are identified. Treatment strategies include alterations in diet and fluid intake as well as drug therapy, all designed to decrease the urine supersaturation.

**Useful For:** Diagnosis and management of patients with renal lithiasis: -In patients who have a
radiopaque stone, for whom stone analysis is not available, the supersaturation data can be used to predict the likely composition of the stone. This may help in designing a treatment program. Individual components of the supersaturation profile can identify specific risk factors for stones. During follow-up, changes in the urine supersaturation can be used to monitor the effectiveness of therapy by confirming that the crystallization potential has indeed decreased. Urine ammonium can be used to evaluate renal excretion of acid and urine pH

**Interpretation:** Delta G (DG), the Gibbs free energy of transfer from a supersaturated to a saturated solution, is negative for undersaturated solutions and positive for supersaturated solutions. In most cases, the supersaturation levels are slightly positive even in normal individuals but are balanced by an inhibitor activity. While the DG of urine is often positive, even in the urine of non-stone formers, on average, the DG is even more positive in those individuals who do form kidney stones. The "normal" values are simply derived by comparing urinary DG values for the important stone-forming crystalline phases between a population of stone formers and a population of non-stone formers. Those DG values that are outside the expected range in a population of non-stone formers are marked "abnormal." A normal or increased citrate value suggests that potassium citrate may be a less effective choice for treatment of a patient with calcium oxalate or calcium phosphate stones. If the urine citrate is low, secondary causes should be excluded including hypokalemia, renal tubular acidosis, gastrointestinal bicarbonate losses (eg, diarrhea or malabsorption), or an exogenous acid load (eg, excessive consumption of meat protein). An increased urinary oxalate value may prompt a search for genetic abnormalities of oxalate production (ie, primary hyperoxaluria). Secondary hyperoxaluria can result from diverse gastrointestinal disorders that result in malabsorption. Milder hyperoxaluria could result from excess dietary oxalate consumption, or reduced calcium (dairy) intake, perhaps even in the absence of gastrointestinal disease. Low urine ammonium and high urine pH suggests renal tubular acidosis. Such patients are at risk of calcium phosphate stones. The results can be used to determine the likely effect of a therapeutic intervention on stone-forming risk. For example, taking oral potassium citrate will raise the urinary citrate excretion, which should reduce calcium phosphate supersaturation (by reducing free ionic calcium), but citrate administration also increases urinary pH (because it represents an alkali load) and a higher urine pH promotes calcium phosphate crystallization. The net result of this or any therapeutic manipulation could be assessed by collecting a 24-hour urine and comparing the supersaturation calculation for calcium phosphate before and after therapy. Important stone-specific factors: -Calcium oxalate stones: Urine volume, calcium, oxalate, citrate, and uric acid excretion are all risk factors that are possible targets for therapeutic intervention. -Calcium phosphate stones (apatite or brushite): Urinary volume, calcium, pH, and citrate significantly influence the supersaturation for calcium phosphate. Of note, a urine pH of less than 6 may help reduce the tendency for these stones to form. -Uric acid stones: Urine pH, volume, and uric acid excretion levels influence the supersaturation. Urine pH is especially critical, in that uric acid is unlikely to crystallize if the pH is greater than 6. -Sodium urate stones: Alkaline pH and high uric acid excretion promote stone formation. A low urine volume is a universal risk factor for all types of kidney stones. The following reference means for calculated supersaturation apply to 24-hour timed collections. No information is available for random collections. Supersaturation Reference Means (Delta G: DG)

**Brushite:** 0.21 DG Hydoxyapatite: 3.96 DG Uric acid: 1.04 DG Sodium urate: 1.76 DG Values for individual analytes that are part of this panel on a random urine collection are best interpreted as a ratio to the creatinine excretion. Following are pediatric reference ranges for the important analytes for which pediatric data is available. Oxalate/Creatinine (mg/mg) Age (year) 95th Percentile 0-0.5 <0.175 0.5-1 <0.139 1-2 <0.103 2-3 <0.08 3-5 <0.064 5-7 <0.056 7-10 <0.048 Matos V, Van Melle G, Werner D, et al: Urinary oxalate and urate to creatinine ratios in a healthy pediatric population. Am J Kidney Dis 1999;34:e1 Uric Acid/Creatinine (mg/mg) Age (year) 95th Percentile 0-0.5 <1.189 <2.378 5-1 <1.040 <2.229 1-2 <0.743 <2.080 2-3 <0.698 <1.932 3-5 <0.594 <1.635 5-7 <0.446 <1.189 7-10 <0.386 <0.832 10-14 >0.297 <0.654 14-17 >0.297 <0.594 Matos V, Van Melle G, Werner D, et al: Urinary oxalate and urate to creatinine ratios in a healthy pediatric population. Am J Kidney Dis 1999;34:e1 Phosphate/Creatinine (mg/mg) Age (year) 95th Percentile 0-0.5 >0.34 <5.24 1-2 >0.34 <3.95 2-3 >0.34 <3.13 3-5 >0.33 <2.17 5-7 >0.33 <1.19 7-10 >0.32 <0.97 10-14 >0.22 <0.86 14-17 >0.21 <0.75 Matos V, van Melle G, Boulat O, et al: Urinary phosphate/creatinine, calcium/creatinine, and magnesium/creatinine ratios in a healthy pediatric population. J Pediatr 1997;131:252-257

Magnesium/Creatinine (mg/g) Age (year) 95th Percentile 0-0.18 1-2 <0.37 2-3 <0.34 3-5 <0.29 5-7 <0.21 7-10 <0.18 10-14 <0.15 14-17 <0.13 Matos V, van Melle G, Boulat O, et al: Urinary phosphate/creatinine, calcium/creatinine, and magnesium/creatinine ratios in a healthy pediatric population. J Pediatr 1997;131:252-257 Citrate/Creatinine (mg/mg) Age (year) 95th Percentile 5-18

**Reference Values:**

**pH:** 4.5-8.0

**Osmolality**

0-11 months: 50-750 mOsm/kg

> or =12 months: 150-1,150 mOsm/kg

**Ammonium**

18-77 years: 3-65 mmol/L

No reference values established for <18 years and >77 years of age

**Calcium**

Random Calcium/Creatinine Ratio:

18-83 years: <0.20 mg/mg

No reference values established for <18 years and >83 years of age

**Magnesium**

Random Magnesium/Creatinine Ratio:

18-83 years: < or =0.035 mg/mg

No reference values established for <18 years and >83 years of age


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**Supplemental Newborn Screen, Blood Spot**

**Clinical Information:** Newborn screening as a public health measure was initiated in the early 1960s for the identification of infants affected with phenylketonuria (PKU). Since then, additional genetic and nongenetic conditions were included in state screening programs. The goal of newborn screening is to detect diagnostic markers of the selected disorders in blood spots collected from presymptomatic newborns. Inherited disorders of amino acid, fatty acid, and organic acid metabolism typically manifest during the first 2 years of life as acute metabolic crises and usually result in severe neurologic impairment or death. These metabolic decompensations are usually triggered by intermittent febrile illness, such as common viral infections leading to prolonged fasting and increased energy demands. Early identification of affected newborns allows for early initiation of treatment to avoid mortality, morbidity, and disabilities due to these disorders. Tandem mass spectrometry (MS/MS) is a powerful multianalyte screening method, which is ideally suited for population-wide testing. Since the early 1990s, MS/MS has made screening possible for more than 30 genetic disorders affecting the metabolism of amino acids, fatty acids, and organic acids based on the profiling of amino acids and acylcarnitines in blood spots. The simultaneous MS/MS analysis of amino acids, acylcarnitines, and succinylacetone in dried blood spots can be performed in less than 3 minutes per specimen, generating metabolite profiles that allow for the biochemical diagnosis of multiple disorders. This is in contrast to conventional screening techniques traditionally based on the principle of 1 separate test for each disorder. In Mayo's experience, the combined incidence of the disorders identifiable by MS/MS in a single blood spot analysis is approximately 1 in 1,700 newborns. Supplemental newborn screening by MS/MS as described here does not replace current state screening programs, because MS/MS does not allow primary screening for galactosemia, congenital hypothyroidism, congenital adrenal hyperplasia (CAH), cystic fibrosis, biotinidase, sickle cell disease, Mucopolysaccharidosis type II, Adrenoleukodystrophy, Pompe disease, severe combined immune deficiency (SCID), critical congenital heart disease, and congenital hearing loss. The Secretary's Advisory Committee on Heritable Disorders...
in Newborns and Children (SACHDNC) recommends all programs screen for 34 core disorders. These conditions are considered to fulfill 3 basic principles: -Condition is identifiable at a period of time (24-48 hours after birth) at which it would not ordinarily be clinically detected. -Test with appropriate sensitivity and specificity is available. -Demonstrated benefits of early detection, timely intervention, and efficacious treatment. *This test does not screen for critical congenital heart disease and congenital hearing loss, both of which are tested in the nursery using methods other than blood spots (audiometry, pulse oximetry). Screening tests do not conclusively determine disease status, but measure analytes which in most cases are not specific for a particular disease. This is the reason why the HHS Secretary also recognizes more than 25 additional conditions as secondary targets that do not meet all inclusion criteria but are identified nevertheless because most of them are components of the differential diagnosis of screening results observed in core conditions. Even for the secondary conditions, the possibility of making a diagnosis early in life not only helps avoid unnecessary diagnostic testing, but is also beneficial to the patient's families because genetic counseling and prenatal diagnosis can be offered. Although not currently in the recommended uniform screening panel, guanidinoacetate methyltransferase (GAMT), a disorder of creatine synthesis, is a condition included in the Mayo Medical Laboratories' supplemental newborn screen. When untreated, this disorder results in a depletion of cerebral creatine leading to global developmental delays, intellectual disability, severe speech delays, and seizures. Patients with GAMT exhibit behavioral problems and features of autism. Treatment consists of lifelong supplementation with creatine monohydrate, ornithine, and dietary protein restriction to decrease cerebral GAA levels. Individuals with GAMT who are treated before the appearance of symptoms may exhibit normal neurodevelopmental outcomes.

**Useful For:** Presymptomatic identification of disorders to allow for early initiation of treatment and consequent improvement in the long-term prognosis of affected patients The conditions identifiable by amino acid and acylcarnitine analysis are detected by supplemental newborn screening using tandem mass spectrometry (MS/MS) as described here. Analyte (assay platform) ACMG Recommended Conditions Additional Conditions/Treatment Detectable by MS/MS Core Condition Secondary Targets Amino Acids (MS/MS) Phe PKU BS HPA REG TPN Leu/Ile, Val MSUD TPN Met HCY Met TPN, nonspecific liver disease Ctc, Arg, ASA ASA CIT ARG CIT-II Tyr TYR-I TYR-II TYR-III Nonspecific liver disease GUAC GAMT Acylcarnitines (MS/MS) C0 HUD Maternal CUD, maternal GA-I, maternal MCAD C3 CblA, Cbl B MUT PA Cbl C, Cbl D C4 IBDH SCAD FIGLU C5 IVA SBCAD Antibiotics containing pivalic acid C5-OH BKT HMG MCC MCD MGA-I MHBD Maternal MCC, biotinidase deficiency C8 MCAD1 GA-II1 MCKAT1 M/SCHAD1 C3-DC MAL C10:2 DR C5-DC GA-I C14:1, C16, C18:1 VLCAD CACT CPT-I2 CPT-II C16-OH LCHAD2 TFP2 m/z 225<399<473 Dextrose infusion m/z 342 (C8:1) Artifact often observed in premature neonates m/z 470 (C16:1OH) Cefotaxime metabolite Succinylacetone TYR-I

**Interpretation:** The quantitative measurements of the various amino acids, acylcarnitines, and succinylacetone support the interpretation of the complete profile but for the most part are not diagnostic by themselves. The interpretation is by pattern recognition. Abnormal results are not sufficient to conclusively establish a diagnosis of a particular disease. To verify a preliminary diagnosis, independent biochemical (ie, in vitro enzyme assay) or molecular genetic analyses are required, many of which are offered within Mayo Clinic's Division of Laboratory Genetics. The reports are in text form only, values for the more than 60 analytes and analyte ratios are not provided. A report for a normal screening result is reported as: "In this blood spot sample, the amino acid and acylcarnitine profiles by tandem mass spectrometry showed no biochemical evidence indicative of an underlying metabolic disorder." A report for an abnormal screening result includes a quantitative result of the abnormal metabolites, a detailed interpretation of the results, including an overview of the results significance, possible differential diagnoses, recommendations for additional biochemical testing and confirmatory studies (enzyme assay, molecular analysis), and a phone number for a contact at Mayo Clinic if the referring physician has additional questions.

**Reference Values:**
An interpretive report is provided

**Clinical References:**

**STPPC**  
**Surg Path Touch Prep (Bill Only)**  
**Reference Values:**  
This test is for billing purposes only.  
This is not an orderable test.

**STAPC**  
**Surg Path Touch Prep Additional (Bill Only)**  
**Reference Values:**  
This test is for billing purposes only.  
This is not an orderable test.

**SUS**  
**Susceptibility (Bill Only)**  
**Reference Values:**  
This test is for billing purposes only.  
This is not an orderable test.

**STV1**  
**Susceptibility, Mtb Complex, Broth (Bill Only)**  
**Reference Values:**  
This test is for billing purposes only.  
This is not an orderable test.

**STVP**  
**Susceptibility, Mtb Complex, PZA (Bill Only)**  
**Reference Values:**  
This test is for billing purposes only.  
This is not an orderable test.

**STV2**  
**Susceptibility, Mtb Cx, 2nd Line (Bill Only)**  
**Reference Values:**  
This test is for billing purposes only.  
This is not an orderable test.

**TBPZA**  
**Susceptibility, Mycobacterium tuberculosis Complex, Pyrazinamide**
Clinical Information: Primary treatment regimens for Mycobacterium tuberculosis complex often include isoniazid, rifampin, ethambutol, and pyrazinamide (PZA). Susceptibility testing of each Mycobacterium tuberculosis complex isolate against these first-line antimycobacterial agents is a key component of patient management. The Clinical and Laboratory Standards Institute (CLSI) provides consensus protocols for the methods, antimycobacterial agents, and critical concentrations of each agent to be tested in order to permit standardized interpretation of Mycobacterium tuberculosis complex susceptibility test results. Current recommendations indicate that laboratories should use a rapid broth method in order to obtain Mycobacterium tuberculosis complex susceptibility data as quickly as possible to help guide patient management. According to the CLSI, resistance can be confirmed by another method or by another laboratory at the discretion of the testing laboratory. This test uses an FDA-cleared commercial system for rapid broth susceptibility testing of Mycobacterium tuberculosis complex against PZA. Since the literature indicates that broth testing of PZA can, at times, produce falsely resistant results, resistance to PZA by the broth method is automatically confirmed by pncA DNA sequencing. The pncA gene of Mycobacterium tuberculosis complex is responsible for activation of the prodrug PZA and hence PZA activity. Mutations in the pncA gene and upstream promoter region have been reported to account for the majority (70%-97%) of PZA-resistant isolates. However, 3% to 30% of PZA-resistant isolates do not have a corresponding pncA mutation and other genes (eg, rpsA) may also play a role. A separate test is available for testing of the other first-line agents (isoniazid, rifampin and ethambutol).

Useful For: Susceptibility testing of Mycobacterium tuberculosis complex isolates growing in pure culture against pyrazinamide Confirming Mycobacterium tuberculosis complex resistance to pyrazinamide

Interpretation: Mycobacterium tuberculosis complex isolates are reported as susceptible or resistant to pyrazinamide at the critical concentration.

Reference Values: Results are reported as susceptible or resistant.

**Susceptibility, Mycobacterium tuberculosis Complex, Second Line**

**Clinical Information:** The Clinical and Laboratory Standards Institute (CLSI) provides a consensus protocol for the methods, antimycobacterial agents, and critical concentrations of each agent to be tested in order to permit standardized interpretation of Mycobacterium tuberculosis complex susceptibility testing results. CLSI guidelines suggest that second-line agents should be tested when an isolate of Mycobacterium tuberculosis complex is resistant to rifampin, is monoresistant to the critical concentration of isoniazid and the physician intends to use a fluoroquinolone for therapy, or is resistant to any combination of 2 first-line agents. This test uses a broth microdilution method for susceptibility testing of Mycobacterium tuberculosis complex against second-line agents. Agents tested are amikacin, cycloserine, ethionamide, kanamycin, moxifloxacin, ofloxacin, p-aminosalicylic acid, rifabutin, and streptomycin. In contrast to other Mycobacterium tuberculosis susceptibility methods which test 1 or 2 critical concentrations of a drug, this method examines a range of drug concentrations and produces an minimal inhibitory concentration result.

**Useful For:** Determination of Mycobacterium tuberculosis complex minimal inhibitory concentrations to second-line antimicrobial agents

**Interpretation:** Results are reported as minimal inhibitory concentrations (MIC) in mcg/mL and tentative interpretations of susceptible or resistant are provided. Agent MIC Range Tested (mcg/mL) MIC Tentative Interpretations (mcg/mL)(1) Susceptible Resistant Amikacin 0.12-16 < or =4.0 >4.0 Cycloserine 2-256 < or =32.0 >32.0 Ethionamide 0.3-40 < or =5.0 >5.0 Kanamycin 0.6-40 < or =5.0 >5.0 Moxifloxacin 0.06-8 < or =2.0 >2.0 Ofloxacin 0.25-32 < or =2.0 >2.0 Para-aminosalicylic acid 0.5-64 < or =0.5 >0.5 Streptomycin 0.25-32 < or =2.0 >2.0 Isoniazid* 0.03-4 < or =0.25 >0.25 Ethambutol* 0.5-32 < or =4 >4 Rifampin* 0.12-16 < or =1 >1

Laboratory-derived tentative interpretations based on MIC breakpoints established relative to the indirect agar proportion method; consensus breakpoint interpretations are not available at this time. (Hall L, Jude KP, Clark SL, et al: Evaluation of the Sensititre MycoTB plate for susceptibility testing of the Mycobacterium tuberculosis complex against first- and second-line agents. J Clin Microbiol 2012;50:3732-3734) *This test is used as an alternative to TB1LN / Antimicrobial Susceptibility, Mycobacterium tuberculosis Complex, First Line when reagents are not available to perform the TB1LN test.

**Reference Values:** Results are reported as minimal inhibitory concentration (MIC) values with units of mcg/mL and tentative interpretations of susceptible or resistant are provided.


**Sweet Gum, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).
Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>Interpretation</th>
</tr>
</thead>
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<tr>
<td>0</td>
<td>Negative</td>
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<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


Sweet Potato, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
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<tr>
<td>5</td>
<td>50.0-99.9</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Table 1: Reference Values

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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</thead>
<tbody>
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<td>0</td>
<td>Negative</td>
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<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
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<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
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<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference</td>
</tr>
</tbody>
</table>


Swordfish, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

Class IgE kU/L Interpretation
0 0.35-0.69 Equivocal
1 0.70-3.49 Positive
2 3.50-17.4 Positive
3 17.5-49.9 Strongly positive
4 50.0-99.9 Strongly positive
5 > or =100 Strongly positive Reference values apply to all ages.


Synaptophysin (SYNAPTO) Immunostain, Technical Component Only

Clinical Information: Synaptophysin is a calcium-binding protein present in the presynaptic vesicles of neurons as well as vesicles in the neuroendocrine cells. Synaptophysin is expressed in neuronal tumors and tumors with neuroendocrine differentiation including neuroblastoma, ganglioneuroblastoma, ganglioneuroma, pheochromocytoma/paraganglioma and carcinoid/neuroendocrine carcinoma. Antibodies to synaptophysin strongly stain the cytoplasm of all the neuroendocrine cells in the pancreatic islets and is
also seen in adrenal cortical cells, probably due to a closely related protein.

**Useful For:** Identification of neuronal tumors and tumors with neuroendocrine differentiation

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**Synovial Sarcoma (SS), 18q11.2 (SS18 or SYT) Rearrangement, FISH, Tissue**

**Clinical Information:** Synovial sarcoma (SS) is a malignant soft tissue tumor that predominantly occurs in the lower limbs of children and young adults. This tumor accounts for approximately 5% to 10% of soft tissue tumors, has a poor prognosis, and may occur in other areas of the body such as the head and neck, heart, abdominal wall, mediastinum, and lung, in addition to the extremities. Histologically, SS is grouped either into the monophasic subtype consisting of mostly spindle cells or the biphasic subtype consisting of epithelial and spindle cells. Depending on the site of origin, the differential diagnosis of SS can include mesothelioma, fibrosarcoma, solitary fibrous tumor, leiomyosarcoma, malignant peripheral nerve sheath tumors, epithelioid sarcoma, and clear cell sarcoma. In addition, when the SS is poorly differentiated, the differential diagnosis broadens to include the small round-blue cell tumors (Ewing sarcoma, alveolar rhabdomyosarcoma, and neuroblastoma). Accurate diagnosis of SS is important for appropriate clinical management of patients. Although immunohistochemical markers can be helpful in the correct diagnosis of these various tumor types, recent molecular studies have shown the superior specificity of molecular makers in differentiating SS from other tumors. A recurrent, tumor-specific translocation t(X;18)(p11.2;q11.2) is observed in approximately 90% of synovial sarcomas. A single gene, SS18 (SYT), has been implicated on 18q11.2, while 1 of 3 related genes, SSX1, SSX2, or infrequently SSX4, is usually involved on Xp11.2. The prevalence of SS18-SSX1 is about twice that of SS18-SSX2 in most studies. Detection of these transcripts is usually performed by reverse transcriptase-PCR (RT-PCR) (SYT / Synovial Sarcoma RT-PCR), which allows specific identification of SS18-SSX1 or SS18-SSX2. Identification of the SS18-SSX1 fusion is associated with an unfavorable outcome with significantly shorter overall survival when compared to the SS18-SSX2 fusion. Unfortunately, RT-PCR results may be equivocal or falsely negative due to many reasons such as when the available RNA is of poor quality or if a rare translocation partner is present. In these cases, FISH testing can be used to identify SS18 gene rearrangements in these tumors, which supports the diagnosis of SS.

**Useful For:** Supporting the diagnosis of synovial sarcoma when used in conjunction with an anatomic pathology consultation

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal cutoff for the SYT FISH probe. A positive result suggests rearrangement of the SYT gene region at 18q11.2 and supports the diagnosis of synovial sarcoma (SS). A negative result suggests no...
rearrangement of the SYT gene region at 18q11.2. However, this result does not exclude the diagnosis of SS.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

### Synovial Sarcoma by Reverse Transcriptase PCR (RT-PCR)

**Clinical Information:** Synovial sarcomas account for 9% to 10% of soft tissue tumors. These tumors occur in 2 major forms: biphasic and monophasic. Monophasic tumors are composed entirely of spindle cells, while biphasic tumors have epithelial cells arranged in glandular structures and mixed with spindle cells. The tumors are usually positive for keratin and epithelial membrane antigen as well as vimentin by immunostaining. Synovial sarcoma is a member of the small round-cell tumor group that includes rhabdomyosarcoma, lymphoma, Wilms tumor, Ewing sarcoma, and desmoplastic small round-cell tumor.

While treatment and prognosis depend on establishing the correct diagnosis, the diagnosis of sarcomas that form the small round-cell tumor group by light microscopic examination alone can be very difficult, especially true when only small-needle biopsy specimens are available for examination. The use of immunohistochemical stains (eg, keratin and epithelial membrane antigen [EMA]) can assist in establishing the correct diagnosis, but these markers are not entirely specific for synovial sarcoma.

Expertise in soft tissue and bone pathology are often needed. Studies have shown that some sarcomas have specific recurrent chromosomal translocations. These translocations produce highly specific gene fusions that help define and characterize subtypes of sarcomas and are useful in the diagnosis of these lesions.(1-4) Cytogenetic studies have shown a distinctive chromosomal translocation, t(X;18)(p11;q11), in more than 90% of synovial sarcomas. Cloning of the translocation breakpoint showed that t(X;18) results in the fusion of 2 genes designated as SS18 (at 18q11) and SSX (at Xp11). Two closely related genes, SSX1 and SSX2, have 81% homology in proteins. SS18-SSX1 is present in 55% of cases, while SS18-SSX2 is present in 35% of cases. Patients with SS18-SSX2 translocation usually have greater metastasis-free survival than those with SS18-SSX1. These fusion transcripts can be detected by reverse transcriptase PCR (RT-PCR), by FISH, chromogenic in situ hybridization (CISH), or by classical cytogenetic analyses. The RT-PCR and FISH procedures are the most sensitive methods to detect these fusion transcripts.(3)

**Useful For:** Supporting a diagnosis of synovial sarcoma

**Interpretation:** A positive SS18-SSX1 or SS18-SSX2 result is consistent with a diagnosis of synovial sarcoma. Sarcomas other than synovial sarcoma, and carcinomas, melanomas, and lymphomas are negative for the fusion products. A negative result does not rule out a diagnosis of synovial sarcoma.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
## Synthetic Cannabinoid Metabolites Screen - Expanded, Urine

### Reference Values:

<table>
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<tr>
<th>Test</th>
<th>Reference Range</th>
<th>Units</th>
<th>Reporting Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>JWH-018 N-pentanoic acid</td>
<td>None Detected</td>
<td>ng/mL</td>
<td>0.20</td>
</tr>
<tr>
<td>Synonym(s): 5-(3-(1-naphthoyl)-1H-indol-1-yl)-pentanoic acid</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>UR-144 N-pentanoic acid</td>
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<td></td>
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<td>Synonym(s): 3-[tricyclo[3.3.1.13,7]dec-1-ylamino]carbonyl]-1H-indazole-1-pentanoic acid; APINACA N-pentanoic acid metabolite</td>
<td></td>
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<td>AB-FUBINACA oxobutanoic acid</td>
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<td>PB-22 3-Carboxyindole</td>
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<tr>
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<td>ADB-PINACA N-pentanoic acid</td>
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<td>AB-PINACA N-pentanoic acid</td>
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<td>ADBICA N-pentanoic acid</td>
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</table>
### Synthetic Glucocorticoid Screen, Serum

**Clinical Information:** Synthetic glucocorticoids are widely used and have important clinical utility both as anti-inflammatory and immunosuppressive agents. The medical use of these agents, as well as their surreptitious use, can sometimes lead to a confusing clinical presentation. Patients exposed to these steroids may present with clinical features of Cushing syndrome, but with suppressed cortisol levels and evidence of hypothalamus-pituitary-adrenal axis suppression. This assay does not detect fluticasone propionate.

**Useful For:** Confirming the presence of listed synthetic glucocorticoids (see Interpretation) Confirming the cause of secondary adrenal insufficiency

**Interpretation:** This test screens for and quantitates, if present, the following synthetic glucocorticoids: betamethasone, budesonide, dexamethasone, fludrocortisone, flunisolide, fluorometholone, megestrol acetate, methylprednisolone, prednisolone, prednisone, triamcinolone, and triamcinolone acetonide. The presence of synthetic glucocorticoids in serum indicates current or recent use of these compounds. Since several of these compounds exceed the potency of endogenous cortisol by 1 or more orders of magnitude, even trace levels may be associated with Cushingoid features.

**Reference Values:**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cutoff Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Budesonide</td>
<td>0.20 mcg/dL</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Substance</td>
<td>Concentration</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Fluorometholone</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Prednisone</td>
<td>0.10 mcg/dL</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>0.30 mcg/dL</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>0.10 mcg/dL</td>
</tr>
</tbody>
</table>

Values for normal patients not taking these synthetic glucocorticoids should be less than the cutoff concentration (detection limit).

**Clinical References:**

**Synthetic Glucocorticoid Screen, Urine**

**Clinical Information:** Synthetic glucocorticoids are widely used and have important clinical utility both as anti-inflammatory and immunosuppressive agents. The medical use of these agents, as well as their surreptitious use, can sometimes lead to a confusing clinical presentation. Patients exposed to these steroids may present with clinical features of Cushing syndrome, but with suppressed cortisol levels and evidence of hypothalamus-pituitary-adrenal axis suppression. The fluticasone propionate analyte is reported with this test and is also available separately, see 17BFP / Fluticasone 17-Beta-Carboxylic Acid, Urine for more information.

**Useful For:**
- Confirming the presence of the listed synthetic glucocorticoids (see Interpretation)
- Confirming the cause of secondary adrenal insufficiency

**Interpretation:** This test screens for and quantitates, if present, the following synthetic glucocorticoids: beclomethasone dipropionate, betamethasone, budesonide, dexamethasone, fludrocortisone, flunisolide, fluorometholone, megestrol acetate, methylprednisolone, prednisolone, prednisone, triamcinolone, and triamcinolone acetonide. The presence of synthetic glucocorticoids in urine indicates current or recent use of these compounds. Since several of these compounds exceed the potency of endogenous cortisol by 1 or more orders of magnitude, even trace levels may be associated with Cushingoid features.

**Reference Values:**

<table>
<thead>
<tr>
<th>Cutoff</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Beclomethasone dipropionate: 0.10 mcg/dL</td>
</tr>
<tr>
<td></td>
<td>Betamethasone: 0.10 mcg/dL</td>
</tr>
<tr>
<td></td>
<td>Budesonide: 0.20 mcg/dL</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone: 0.10 mcg/dL</td>
</tr>
<tr>
<td></td>
<td>Fludrocortisone: 0.10 mcg/dL</td>
</tr>
<tr>
<td></td>
<td>Flunisolide: 0.10 mcg/dL</td>
</tr>
<tr>
<td></td>
<td>Fluorometholone: 0.10 mcg/dL</td>
</tr>
<tr>
<td></td>
<td>Megestrol acetate: 0.10 mcg/dL</td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone: 0.10 mcg/dL</td>
</tr>
<tr>
<td></td>
<td>Prednisolone: 0.10 mcg/dL</td>
</tr>
<tr>
<td></td>
<td>Prednisone: 0.10 mcg/dL</td>
</tr>
<tr>
<td></td>
<td>Triamcinolone 0.30 mcg/dL</td>
</tr>
<tr>
<td></td>
<td>Triamcinolone acetonide: 0.10 mcg/dL</td>
</tr>
</tbody>
</table>

Current as of October 11, 2018 2:20 pm CDT 800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Values for normal patients not taking these synthetic glucocorticoids should be less than the cutoff concentration (detection limit).


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**TPPA**

61480

**Syphilis Antibody by TP-PA, Serum**

**Clinical Information:** Syphilis is a disease caused by infection with the spirochete Treponema pallidum. The infection is systemic and the disease is characterized by periods of latency. These features, together with the fact that T pallidum cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis. Syphilis is categorized by an early primary infection in which patients may have non-specific symptoms, and potentially, genital lesions. Patients tested by serology during the primary phase may be negative for antibodies, especially if testing is performed during the first 1 to 2 weeks after symptom onset. As the disease progresses into the secondary phase, antibodies to T pallidum reach peak titers, and may persist indefinitely regardless of the disease state or prior therapy. Therefore, detection of antibodies to nontreponemal antigens, such as cardiolipin (a lipoidal antigen released by host cells damaged by T pallidum) may help to differentiate between active and past syphilis infection. Nontreponemal antibodies are detected by the rapid plasma reagin (RPR) assay, which is typically positive during current infection and negative following treatment or during late-latent forms of syphilis. For prenatal syphilis screening, the syphilis IgG test (SYPGN / Syphilis Antibody, IgG, Serum) is recommended. Testing for IgM-class antibodies to T pallidum should not be performed during routine pregnancy screening unless clinically indicated. Historically, the serologic testing algorithm for syphilis included an initial nontreponemal screening test, such as the RPR or the venereal disease research laboratory (VDRL) tests. Because these tests measure the host's antibody response to nontreponemal antigens, they may lack specificity. Therefore, a positive result by RPR or VDRL requires confirmation by a treponemal-specific test, such as the fluorescent treponemal antibody-absorbed (FTA-ABS) or the T pallidum particle agglutination (TP-PA). Although the FTA-ABS and TP-PA are technically simple to perform, they are labor intensive and require subjective interpretation by testing personnel. Due to the low prevalence of syphilis in the United States, the increased specificity of treponemal assays, and the objective interpretation of automated treponemal enzyme immunoassay (EIA) and multiplex flow immunoassays (MFI), many large clinical laboratories have switched to screening for syphilis using a reverse algorithm. Per this algorithm, serum samples are first tested by an automated treponemal assay (eg, EIA or MFI). Specimens testing positive by these assays are then reflexed to the RPR assay to provide an indication of the patient's disease state and history of treatment. Recently, the Centers for Disease Control and Prevention recommended that specimens testing positive by a screening treponemal assay and negative by RPR be tested by a second treponemal test (eg, TP-PA). The results of TP-PA assist in determining whether the results of a screening treponemal test are truly or falsely positive.

**Useful For:** An aid to resolve discrepant results between screening treponemal (eg, enzyme immunoassay [EIA], multiplex flow immunoassay) and nontreponemal (eg, rapid plasma reagin) assays

**Interpretation:** Syphilis screening at Mayo Clinic is performed by using the reverse algorithm, which first tests sera for Treponema pallidum specific IgG antibodies using an automated multiplex flow immunoassay (MFI). (3) IgG antibodies to syphilis can remain elevated despite appropriate antimicrobial treatment and a reactive result does not distinguish between recent or past infection. To further evaluate disease and treatment status, samples that are reactive by the syphilis IgG screening test are reflexed to the rapid plasma reagin (RPR) assay, which detects antibodies to cardiolipin, a lipoidal antigen released from host cells damaged by T pallidum. (2) Unlike treponemal-specific antibodies, RPR titers decrease and
usually become undetectable following appropriate treatment and can be used to monitor response to therapy. In some patients, the results of the treponemal screening test (syphilis IgG) and RPR may be discordant (eg, syphilis IgG positive and RPR negative). To discriminate between a falsely reactive screening result and past syphilis, the Centers for Disease Control and Prevention recommends performing a second treponemal-specific antibody test using a method that is different from the initial screening test (eg, T pallidum particle agglutination: TP-PA). (2) In the setting of a positive syphilis IgG screening result and a negative RPR, a positive TP-PA result is consistent with either 1) past, successfully treated syphilis, 2) early syphilis with undetectable RPR titers, or 3) late/latent syphilis in patients who do not have a history of treatment for syphilis. Further historical evaluation is necessary to distinguish between these scenarios (Table 1). In the setting of a positive syphilis IgG screening result and a negative RPR, a negative TP-PA result is most consistent with a falsely reactive syphilis IgG screen (Table 1). If syphilis remains clinically suspected, a second specimen should be submitted, order SYGR / Syphilis IgG Antibody with Reflex, Serum. Table 1. Interpretation and follow-up of reverse screening results Patient history Test and result Interpretation Follow-up EIA/CIA/MFI RPR TP-PA Unknown history of syphilis Non-reactive N/A N/A No serologic evidence of syphilis None, unless clinically indicated (eg, early syphilis) Unknown history of syphilis Reactive Reactive N/A Untreated or recently treated syphilis See CDC treatment guidelines Unknown history of syphilis Reactive Non-reactive Non-reactive Probable false-positive screening test No follow-up testing, unless clinically indicated Unknown history of syphilis Reactive Non-reactive Reactive Possible syphilis (eg, early or latent) or previously treated syphilis Historical and clinical evaluation required Known history of syphilis Reactive Non-reactive Reactive or N/A Past, successfully treated syphilis None CIA, chemiluminescence immunoassay; EIA, enzyme immunoassay; MFI, multiplex flow immunoassay; N/A, not applicable; RPR, rapid plasma reagin; TP-PA, Treponema pallidum particle agglutination. http://www.cdc.gov/std/treatment/2010/

Reference Values:
Negative


Syphilis Antibody, IgG, Serum

Clinical Information: Syphilis is a disease caused by infection with the spirochete Treponema pallidum. The infection is systemic and the disease is characterized by periods of latency. These features, together with the fact that Treponema pallidum cannot be isolated in culture, mean that serologic techniques play a major role in the diagnosis and follow-up of treatment for syphilis. Historically, the serologic testing algorithm for syphilis included an initial nontreponemal screening test, such as the rapid plasma reagin (RPR) or the venereal disease research laboratory (VDRL) tests. Because these tests measure the host's antibody response to nontreponemal antigens, they lack specificity. Therefore, a positive result by RPR or VDRL requires confirmation by a treponemal-specific test, such as the fluorescent treponemal antibody-absorbed (FTA-ABS) or microhemagglutination assay (MHA-TP). Although the FTA-ABS and MHA-TP are technically simple to perform, they are labor intensive and require subjective interpretation by testing personnel. Recently, EIA and multiplex flow immunoassays (MFI) were introduced to assess serologic response to Treponema pallidum. The Bio-Rad BioPlex Syphilis IgG assay is an example of MFI technology, which utilizes specific, treponemal antigens coated on microspheres for the detection of IgG-class antibodies to Treponema pallidum. The BioPlex Syphilis IgG assay is highly sensitive and specific (see Supportive Data), and allows for an objective interpretation of results. Due to several factors including the low prevalence of syphilis in the United States, the increased specificity of treponemal assays, and the objective interpretation of MFI and EIA technology, initial serologic testing by a treponemal-specific assay (eg, EIA or MFI) is now commonly performed in clinical laboratories. Specimens testing positive by the treponemal-specific assay are then tested by RPR to provide supplementary serologic data, as
well as to provide an indication of the patient’s disease state and history of treatment. During early primary syphilis, the first antibodies to appear are of the IgM-class, with IgG-class antibodies reaching significant titers later in the primary phase. As the disease progresses into the secondary phase, IgG-class antibodies to Treponema pallidum reach peak titers, and may persist indefinitely regardless of the disease state or prior therapy. For prenatal syphilis screening, the IgG test is recommended. IgM testing should not be performed during routine pregnancy screening unless clinically indicated. Treponema pallidum IgG antibodies persist indefinitely, regardless of the course of the disease. If treatment of an original Treponema pallidum infection was not monitored, a diagnosis of reinfection may actually represent either a resurgence of an inadequately treated earlier infection or persistent IgG antibodies from a resolved infection.

**Useful For:** An aid in the diagnosis of active Treponema pallidum infection Routine prenatal screening

**Interpretation:** A positive IgG treponemal test suggests infection with Treponema pallidum at some point in the past, but does not distinguish between treated and untreated infections. This is because treponemal tests (eg, EIA, multiplex flow immunoassay, or fluorescent treponemal antibody-absorbed) may remain reactive for life, even following adequate therapy. Therefore, the results of a nontreponemal assay, such as rapid plasma reagin, are needed to provide information on a patient's disease state and history of therapy.

**Reference Values:**
Negative

**Useful For:** Aiding in the diagnosis of active Treponema pallidum infection Routine prenatal screening

**Interpretation:** Syphilis screening at Mayo Clinic is performed by using the reverse algorithm, which first tests sera for Treponema pallidum-specific IgG antibodies using an automated multiplex flow immunoassay (MFI). A positive IgG treponemal test suggests infection with T pallidum at some point in the past, but does not distinguish between treated and untreated infections. This is because treponemal tests (eg, EIA, MFI, or fluorescent treponemal antibody-absorbed: FTA-ABS) may remain reactive for life, even following adequate therapy. Therefore, the results of a nontreponemal assay, such as rapid plasma reagin (RPR), are needed to provide information on a patient's disease state and history of therapy. In some patients, the results of the treponemal screening test (syphilis IgG) and RPR may be discordant (eg, syphilis IgG positive and RPR negative). To discriminate between a falsely reactive screening result and past syphilis, CDC recommends performing a second treponemal-specific antibody test using a method that is different from the initial screen test (eg, T pallidum particle agglutination: TP-PA). (1) In the setting of a positive syphilis IgG screening result and a negative RPR, a positive TP-PA result is consistent with either 1) past, successfully treated syphilis, 2) early syphilis with undetectable RPR titers, or 3) late/latent syphilis in patients who do not have a history of treatment for syphilis. Further historical evaluation is necessary to distinguish between these scenarios. (Table 1) In the setting of a positive syphilis IgG screening result and a negative RPR, a negative TP-PA result is most consistent with a falsely reactive syphilis IgG screen (Table 1). If syphilis remains clinically suspected, a second specimen should be submitted for testing. Equivocal: Recommend follow-up testing in 10 to 14 days if clinically indicated. Table 1. Interpretation and follow-up of reverse screening results: Test and result Patient history EIA/CIA/MFI RPR TP-PA Interpretation Follow-up Unknown history of syphilis Nonreactive NA NA No serologic evidence of syphilis None, unless clinically indicated (eg, early syphilis) Unknown history of syphilis Reactive NA Untreated or recently treated syphilis See CDC treatment guidelines Unknown history of syphilis Reactive Nonreactive False-positive screening test No follow-up testing, unless clinically indicated Unknown history of syphilis Reactive Nonreactive Reactive Possible syphilis (eg, early or latent) or previously treated syphilis Historical and clinical evaluation required Unknown history of syphilis Equivocal NA NA NA Recommend follow-up testing in 10 to 14 days if clinically indicated Known history of syphilis Reactive Nonreactive Reactive or N/A Past, successfully treated syphilis None CIA, chemiluminesence immunoassay; EIA, enzyme immunoassay; MFI, multiplex flow immunoassay; NA, not applicable; RPR, rapid plasma reagin; TP-PA, Treponema pallidum particle agglutination. 

www.cdc.gov/std/treatment/2010/

**Reference Values:**

Negative


**T, B and NK Lymphocyte Quantitation, New York**

**Clinical Information:** Lymphocytes in peripheral blood (circulation) are heterogeneous and can be broadly classified into T cells, B cells, and natural killer (NK) cells. There are various subsets of each of these individual populations with specific cell-surface markers and function. This assay provides absolute (cells/mL) and relative (%) quantitation for the main categories of T cells, B cells, and NK cells, in addition to a total lymphocyte count (CD45+). Each of these lymphocyte subpopulations have distinct effector and regulatory functions and are maintained in homeostasis under normal physiological conditions. Each of these lymphocyte subsets can be identified by a combination of 1 or more cell surface markers. The CD3 antigen is a pan-T cell marker, and T cells can be further divided into 2 broad categories, based on the expression of CD4 or CD8 coreceptors. B cells can be identified by expression...
of CD19, while NK cells are typically identified by the coexpression of CD16 and CD56. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 a.m. and noon with no change between noon and afternoon. NK-cell counts, on the other hand, are constant throughout the day. Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration. (2-4) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naïve versus effector CD4 and CD8 T cells. (2) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared to the evening (5) and during summer compared to winter. (6) These data therefore indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets. Abnormalities in the number and percent of T (CD3+, CD4+, CD8+), B (CD19), and NK (CD16+CD56) lymphocytes have been described in a number of different disease conditions. In patients who are infected with HIV, the CD4 count is measured for AIDS diagnosis and for initiation of antiviral therapy. The progressive loss of CD4 T-lymphocytes in patients infected with HIV is associated with increased infections and complications. The Public Health Service has recommended that all HIV-positive patients be tested every 3 to 6 months for the level of CD4 T-lymphocytes. Lymphocyte subset quantitation is also very useful in the evaluation of patients with primary immunodeficiencies of all ages, including follow-up for newborn screening for severe combined immunodeficiency and immune monitoring following immunosuppressive therapy for transplantation, autoimmunity or any other relevant clinical condition where immunomodulatory treatment is used. It is also helpful as a preliminary screening assay for gross quantitative anomalies in any lymphocyte subset, whether related to malignancies or infection. The 2008 guidelines for diagnosis and treatment of chronic lymphocytic leukemia (CLL) from the International Workshop on Chronic Lymphocytic Leukemia (7) recommend changing the diagnostic criteria for CLL from an absolute lymphocyte count greater than 5 x 10^9/L to a circulating B-cell count greater than 5 x 10^9/L (8, 9) previously defined in the 1996 National Cancer Institute guidelines for CLL. This flow cytometric assay enables accurate quantitation of circulating B cells using a single platform technology with absolute quantitation through the use of flow cytometry beads.

**Useful For:** Only orderable by New York clients Serial monitoring of CD4 T-cell count in HIV-positive patients Follow-up and diagnostic evaluation of primary immunodeficiencies, including severe combined immunodeficiency Immune monitoring following immunosuppressive therapy for transplantation, autoimmunity, and other immunological conditions where such treatment is utilized Assessment of immune reconstitution posthematopoietic cell transplantation Early screening of gross quantitative anomalies in lymphocyte subsets in infection or malignancies Absolute quantitation of circulating B cells for diagnosis of chronic lymphocytic leukemia patients as indicated in the 2008 International Workshop on Chronic Lymphocytic Leukemia guidelines

**Interpretation:** HIV treatment guidelines from the US Department of Health and Human Services and the International Antiviral Society-USA Panel recommend antiviral treatment in all patients with HIV infection, regardless of CD4 T-cell count. (10, 11) Additionally, antibiotic prophylaxis for Pneumocystis jiroveci infection and other opportunistic infections is recommended for patients with CD4 count less than 200 cells/mcL.

**Reference Values:** The appropriate age-related reference values will be provided on the report.

**TBET**

**T-Box Expressed in T Cells (TBET) Immunostain, Technical Component Only**

**Clinical Information:** The T-box transcription factor, TBET, is a master regulator of Th1 lymphoid development. It is expressed in other hematopoietic cells including stem cells, B cells, and natural killer cells. In normal tonsil, TBET staining is seen in scattered small interfollicular T lymphocytes, with virtually no staining in the germinal centers. It is preferentially positive in T-cell lymphomas with Th1 differentiation, B-cell lymphomas of memory B-cell origin, and both classical and nodular lymphocyte predominant Hodgkin lymphoma.

**Useful For:** Classification of lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**TALLF**

**T-Cell Acute Lymphoblastic Leukemia (T-ALL), FISH**

**Clinical Information:** In the United States, the incidence of acute lymphoblastic leukemia (ALL) is roughly 6,000 new cases per year (as of 2009), or approximately 1 in 50,000. ALL accounts for approximately 70% of all childhood leukemia cases (ages 0 to 19 years), making it the most common type of childhood cancer. Approximately 85% of pediatric cases of ALL are B-cell lineage (B-ALL) and 15% are T-cell lineage (T-ALL). T-ALL is more common in adolescents than younger children and accounts for 25% of adult ALL. When occurring as a primary lymphoblastic lymphoma (LBL), approximately 90% are T-cell lineage versus only 10% B-cell lineage. T-LBL often present as a mediastinal mass in younger patients with or without concurrent bone marrow involvement. Specific genetic abnormalities are identified in the majority of cases of T-ALL, although many of the classic abnormalities are "cryptic" by conventional chromosome studies and must be identified by FISH studies. Each of the genetic subgroups are important to detect and can be critical prognostic markers.
One predictive marker, amplification of the ABL1 gene region, has been identified in 5% of T-ALL, and these patients may be responsive to targeted tyrosine kinase inhibitors. A combination of cytogenetic and FISH testing is currently recommended in all pediatric and adult patients to characterize the T-ALL clone for the prognostic genetic subgroups. A summary of the characteristic chromosome abnormalities identified in T-ALL are listed in the following table.

Common Chromosome Abnormalities in T-cell Acute Lymphoblastic Leukemia

<table>
<thead>
<tr>
<th>Cytogenetic change</th>
<th>Genes involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>del(1p33)</td>
<td>TAL1/STIL</td>
</tr>
<tr>
<td>t(5;14)(q35;q32)</td>
<td>TLX3(HOX11L2)/BCL11B</td>
</tr>
<tr>
<td>t(10;11)(p13;q14)</td>
<td>MLLT10(AF10)/PICALM</td>
</tr>
<tr>
<td>t(4;11)(q21;q23)</td>
<td>ABL1</td>
</tr>
<tr>
<td>t(11;19)(q23;p13.3)</td>
<td>MLL(KMT2A)/MLLT1(ENL)</td>
</tr>
<tr>
<td>t(7q34;var)</td>
<td>MYB/TRB</td>
</tr>
<tr>
<td>t(7;10)(q34;q24)</td>
<td>TRB/LMO1</td>
</tr>
<tr>
<td>t(11;14)(p15;q11.2)</td>
<td>LMO1/TRAD</td>
</tr>
<tr>
<td>t(11;14)(p13;q11.2)</td>
<td>LMO2/TRAD</td>
</tr>
<tr>
<td>del(9p)</td>
<td>CDKN2A(p16)</td>
</tr>
<tr>
<td>t(10;11)(p13;q23)</td>
<td>MLLT10(AF10)/MLL(KMT2A)</td>
</tr>
<tr>
<td>t(11;19)(q23;p13.3)</td>
<td>MLL(KMT2A)/MLLT1(ENL)</td>
</tr>
<tr>
<td>t(6;11)(q27;q23)</td>
<td>MLLT3(AF9)/MLL(KMT2A)</td>
</tr>
<tr>
<td>t(10;11)(p13;q23)</td>
<td>MLLT10(AF10)/MLL(KMT2A)</td>
</tr>
<tr>
<td>t(11;19)(q23;p13.1)</td>
<td>MLL(KMT2A)/ELL</td>
</tr>
<tr>
<td>t(11;19)(p12;q13.3)</td>
<td>MLL(KMT2A)/MLLT1(ENL)</td>
</tr>
<tr>
<td>t(7q34;var)</td>
<td>MYC/TRAD</td>
</tr>
<tr>
<td>t(11;14)(q11.2:var)</td>
<td>TRAD</td>
</tr>
<tr>
<td>t(7;11)(q34;p13)</td>
<td>TRB/LMO2</td>
</tr>
<tr>
<td>t(8;14)(q24.1;q11.2)</td>
<td>MYC/TRAD</td>
</tr>
<tr>
<td>t(7;11)(q34;p13)</td>
<td>TRB/LMO2</td>
</tr>
<tr>
<td>t(14q11.2:var)</td>
<td>TRAD</td>
</tr>
<tr>
<td>t(10;11)(q24;q11.2)</td>
<td>LXL1(HOX11)</td>
</tr>
<tr>
<td>t(11;14)(p15;q11.2)</td>
<td>LMO1/TRAD</td>
</tr>
<tr>
<td>t(11;14)(p13;q11.2)</td>
<td>LMO2/TRAD</td>
</tr>
<tr>
<td>del(17p)</td>
<td>TP53 Complex karyotype (&gt; or =4 abnormalities)</td>
</tr>
</tbody>
</table>

**Useful For:** Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with T-cell acute lymphoblastic leukemia (T-ALL). Identifying and tracking known chromosome abnormalities in patients with T-ALL and tracking response to therapy. An adjunct to conventional chromosome studies in patients with T-ALL.

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**TIA1**

**T-Cell Intracellular Antigen 1 (TIA-1) Immunostain, Technical Component Only**

**Clinical Information:** T-cell intracellular antigen 1 (TIA-1) shows a granular cytoplasmic staining pattern due to its presence in cytotoxic granules. It is involved in cytotoxic cell-mediated immune responses. TIA-1 was first identified in cytotoxic T cells; it is also expressed in normal natural killer (NK) cells and granulocytes. TIA-1 antibody is useful in characterizing neoplasms of cytotoxic T cells or NK cells.

**Useful For:** Characterizing neoplasms of cytotoxic T cells or natural killer cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of the lab's current practice. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is...
required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**TCL1A**

**T-Cell Leukemia/Lymphoma Protein 1A (TCL1A) Immunostain, Technical Component Only**

**Clinical Information:** T-cell leukemia/lymphoma (TCL) proteins augment AKT signal transduction and enhance cell proliferation and survival. Inversion or translocations involving the TCL-1 gene are present in more than 90% of T-cell prolymphocytic leukemias, resulting in overexpression of the TCL-1 protein. TCL-1 is also found in plasmacytoid monocytes in reactive tissues, and the putative malignant counterpart, blastic plasmacytoid dendritic cell neoplasm. In normal tonsil, expression is limited to the B-cell compartment.

**Useful For:** Identification of T-cell leukemia and lymphoma protein overexpression in neoplasms

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**TLPF**

**T-Cell Lymphoma, FISH, Blood or Bone Marrow**

**Clinical Information:** T-cell neoplasms are relatively uncommon, accounting for approximately 12% of all non-Hodgkin lymphomas. There are several subtypes of T-cell neoplasms: T-cell acute lymphoblastic leukemia (T-ALL), T-cell prolymphocytic leukemia (T-PLL), T-cell large granular lymphocytic leukemia (T-LGL), anaplastic large cell lymphoma (ALCL), peripheral T-cell lymphoma, and various other cutaneous, nodal, and extranodal lymphoma subtypes. The 2 most prevalent lymphoma subtypes are unspecified peripheral T-cell lymphoma (3.7%) and ALCL (2.4%). T-cell neoplasms are among the most aggressive of all hematologic and lymphoid neoplasms with the exception of ALCL, which is usually responsive to chemotherapy. There are a few common
chromosome abnormalities associated with specific subtypes, which this FISH test can detect:
-inv(14)(q11q32) and t(14;14)(q11;q32), which involve the T-cell leukemia/lymphoma 1 gene (TCL1A) and have been associated with T-PLL. Isochromosome 7q and trisomy 8, which have been associated with hepatosplenic T-cell lymphoma. These probes have diagnostic relevance and can also be used to track response to therapy. This assay detects chromosome abnormalities observed in the blood and bone marrow of patients with T-cell lymphoma (for patients with T-cell acute leukemia, order TALLF / T-Cell Acute Lymphoblastic Leukemia [T-ALL], FISH).

Useful For: Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with various T-cell lymphomas. Tracking known chromosome abnormalities and response to therapy in patients with T-cell lymphoma.

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. Detection of an abnormal clone supports a diagnosis of a T-cell lymphoma. The specific abnormality detected may help subtype the neoplasm. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References:

T-Cell Lymphoma, FISH, Tissue

Clinical Information: T-cell malignancies account for approximately 12% of all non-Hodgkin lymphomas. There are several subtypes of T-cell neoplasms: T-cell acute lymphoblastic leukemia (T-ALL), T-cell prolymphocytic leukemia (T-PLL), T-cell large granular lymphocytic leukemia (T-LGL), anaplastic large cell lymphoma (ALCL), peripheral T-cell lymphoma, and various other cutaneous, nodal, and extrandodal lymphoma subtypes. The 2 most prevalent lymphoma subtypes are unspecified peripheral T-cell lymphoma (3.7%) and ALCL (2.4%). A few common chromosome abnormalities are associated with specific T-cell lymphoma subtypes, including: -inv(14)(q11q32) and t(14;14)(q11;q32) involving the T-cell leukemia/lymphoma 1 gene (TCL1A) at 14q32 -Translocations involving the ALK gene at 2p23 in ALCL -Isochromosome 7q and trisomy 8 in hepatosplenic T-cell lymphoma

Useful For: Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with various T-cell lymphomas. Tracking known chromosome abnormalities and response to therapy in patients with T-cell lymphomas.

Interpretation: A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe. Detection of an abnormal clone is supportive of a diagnosis of a T-cell lymphoma. The specific abnormality detected may help subtype the neoplasm. The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Reference Values:
An interpretive report will be provided.

Clinical References:
TCRF1  
**T-Cell Receptor Beta (TCR Beta F1) Immunostain, Technical Component Only**

**Clinical Information:** T-cell receptor beta (TCR Beta F1) antibody is directed against the beta chain of the alpha/beta T-cell receptor, thus staining the majority of T lymphocytes. Staining is localized at cell membranes with weak cytoplasmic staining in some cells. Positive staining in malignant lymphomas can confirm T-cell lineage and further subtype as alpha/beta T cells.

**Useful For:** Classification of lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


TCRGD  
**T-Cell Receptor Delta Immunostain, Technical Component Only**

**Clinical Information:** T-cell receptor delta expression is seen in a small proportion of total T cells. Recognition of T-cell lymphomas that are derived from the delta T-cell subset is important as they often have a more aggressive clinical behavior. Normal tonsils show scattered cells staining in the interfollicular regions.

**Useful For:** Classification of lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


T-Cell Receptor Excision Circles (TREC) Analysis, Blood

Clinical Information: T cell reconstitution is a critical feature of the recovery of the adaptive immune response and has 2 main components: thymic output of new T cells and peripheral homeostatic expansion of preexisting T cells. It has been shown that though thymic function declines with age, a reasonable output is still maintained into late adult life.(1) In many clinical situations, thymic output is crucial to the maintenance and competence of the T cell effector immune response. Thymic function can be determined by T-cell receptor excision circle (TREC) analysis. TREC are extrachromosomal DNA byproducts of T-cell receptor (TCR) rearrangement, which are nonreplicative. TREC are expressed only in T cells of thymic origin and each cell is thought to contain a single copy of TREC. Hence, TREC analysis provides a very specific assessment of T-cell recovery (eg, after hematopoietic cell transplantation) or numerical T-cell competence. There are several TREC generated during the process of TCR rearrangement and the TCR delta deletion TREC (deltaREC psi-J-alpha signal joint TREC) has been shown to be the most accurate TREC for measuring thymic output.(2) This assay measures this specific TREC using quantitative, real-time PCR. Clinical use of TREC in HIV and Antiretroviral Therapy: HIV infection leads to a decrease in thymic function. Adult patients treated with highly active antiretroviral therapy (HAART) show a rapid and sustained increase in thymic output.(1) Clinical use of TREC in Hematopoietic Cell Transplantation (HCT) and Primary Immunodeficiencies (PID): Following HCT, there is a period of prolonged immunodeficiency that varies depending on the nature and type of stem cell graft used and the conditioning regimen, among other factors. This secondary immunodeficiency also includes defects in thymopoiesis.(3-5) It has been shown that numerical T cell recovery is usually achieved by day 100 posttransplant, though there is an inversion of the CD4:CD8 ratio that can persist for up to a year.(4) Also, recovery of T-cell function and diversity can take up to 12 months, although this can be more rapid in pediatric patients. However, recovery of T-cell function is only possible when there is numerical reconstitution of T cells. T cells, along with the other components of adaptive immunity, are key players in the successful response to vaccination post-HCT.(6) Recently, it has been shown in patients who received HCT for severe combined immunodeficiency (SCID) that T cell recovery early after stem cell transplant is crucial to long-term T cell reconstitution.(7) Patients who demonstrated impaired reconstitution were shown to have poor early grafting, as opposed to immune failure caused by accelerated loss of thymic output or long-term graft failure. In this study, the numbers of TREC early after HCT were most predictive for long-term reconstitution. This data suggests that frequent monitoring of T-cell immunity and TREC numbers after HCT can help identify patients who will fail to reconstitute properly, which would allow additional therapies to be instituted in a timely manner.(7) It would be reasonable to extrapolate such a conclusion to other diseases that are also treated by HCT. TREC Copies and Thymic Output in Adults: Since the adult thymus involutes after puberty and is progressively replaced by fat with age, thymus-dependent T cell recovery has been assumed to be severely limited in adults. However, with TREC analysis it has been shown that the change in thymic function in adults is a quantitative phenomenon rather than a qualitative one and thymic output is not totally eliminated.(1,8,9) Thus, after HCT or HAART, the remaining thymic tissue can be mobilized in adults to replenish depleted immune systems with a potentially broader repertoire of naive T cells. Douek et al have shown that there is a significant contribution by the thymus to immune reconstitution after myeloablative chemotherapy and HCT in adults.(8) In fact, this data shows that there is both a marked increase in the TREC numbers and a significant negative correlation of TREC copies with age posttransplant. In addition to the specific clinical situations elucidated above, TREC analysis can be helpful in identifying patients with primary immunodeficiencies and assessing their numerical T-cell immune competence. It can also be used as a measure of immune competence in patients receiving immunotherapy or cancer vaccines, where maintenance of, T-cell output is integral to the immune response against cancer. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have
demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer (NK) cell counts, on the other hand, are constant throughout the day.(10) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration.(11-13) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells.(11) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening.(14) and during summer compared to winter.(15) These data, therefore, indicate that timing and consistency in timing of blood collection are critical when serially monitoring patients for lymphocyte subsets.

**Useful For:** Measuring T-cell output or reconstitution (thymopoiesis) following hematopoietic cell transplantation or highly active antiretroviral therapy Evaluating thymic function in patients with cellular or combined primary immunodeficiencies, or receiving immunotherapy or cancer vaccines Assessing T-cell recovery following thymus transplants for DiGeorge syndrome

**Interpretation:** T-cell receptor excision circles (TRECs) generally show an inverse correlation with age, though there can be substantial variations in TREC copies relative to T-cell count within a given age group. Following hematopoietic cell transplantation (HCT), highly active antiretroviral therapy (HAART), thymic transplants, etc, TREC typically increases from absent or very low levels (below age-matched reference range) to baseline levels or exceeds baseline levels, showing evidence of thymic rebound, which is consistent with recovery of thymic output and T-cell reconstitution. When a patient is being monitored for thymic recovery posttransplant treatment, this assay recommends that a pretransplant (prior to myeloablative or nonmyeloablative conditioning) or a pretreatment baseline specimen be provided so that appropriate comparisons can be made between the pre- and posttransplant treatment specimens. Since there is substantial variability between individuals in TREC copies, the best comparison is made to the patient's own baseline specimen rather than the reference range (which provides a guideline for TREC copies for age-matched healthy controls). A consultative report will be generated for each patient.

**Reference Values:**
The appropriate age-related reference values will be provided on the report.

**Clinical References:**
Clinical Information: The T-cell receptor (TCR) genes (alpha, beta, delta, and gamma) are comprised of numerous, discontinuous coding segments that somatically rearrange to produce heterodimeric cell surface T-cell receptors, either alpha/beta (90%-95% of T cells) or gamma/delta (5%-10% of T cells). With rare exceptions (eg, some neoplastic B-lymphoid proliferations), other cell types retain the "germline" configuration of the TCR genes without rearrangement. The marked diversity of somatic TCR-gene rearrangements is important for normal immune functions, but also serves as a valuable marker to distinguish abnormal T-cell proliferations from reactive processes. A monoclonal expansion of a T-cell population will result in the predominance of a single TCR-gene rearrangement pattern. In contrast, reactive T-cell expansions are polyclonal (or multiclonal), with no single clonotyypic population predominating in the population of T cells. These distributive differences in both TCR sequence and genomic rearrangement fragment sizes can be detected by molecular techniques (ie, PCR) and used to determine if a population of T cells shows monoclonal or polyclonal features.

Useful For: Determining whether a T-cell population is polyclonal or monoclonal

Interpretation: An interpretive report will be provided. Results will be characterized as positive, negative, or indeterminate for a clonal T-cell population. In the appropriate clinicopathologic setting, a monoclonal result is associated with a neoplastic proliferation of T cells (see Cautions).

Reference Values:
An interpretive report will be provided.
Positive, negative, or indeterminate for a clonal T-cell population

Clinical References:
An interpretive report will be provided.
Positive, negative, or indeterminate for a clonal T-cell population


**TCGRV** 31140

**T-Cell Receptor Gene Rearrangement, PCR, Varies**

**Clinical Information:** The T-cell receptor (TCR) genes (alpha, beta, delta, and gamma) are comprised of numerous, discontinuous coding segments that somatically rearranged to produce heterodimeric cell surface T-cell receptors, either alpha/beta (90%-95% of T cells) or gamma/delta (5%-10% of T cells). With rare exceptions (eg, some neoplastic B-lymphoid proliferations), other cell types retain the "germline" configuration of the TCR genes without rearrangement. The marked diversity of somatic TCR-gene rearrangements is important for normal immune functions, but also serves as a valuable marker to distinguish abnormal T-cell proliferations from reactive processes. A monoclonal expansion of a T-cell population will result in the predominance of a single TCR-gene rearrangement pattern. In contrast, reactive T-cell expansions are polyclonal (or multiclonal), with no single clonotypic population predominating in the population of T cells. These distributive differences in both TCR sequence and genomic rearrangement fragment sizes can be detected by molecular techniques (ie, PCR) and used to determine if a population of T cells shows monoclonal or polyclonal features.

**Useful For:** Determining whether a T-cell population is polyclonal or monoclonal

**Interpretation:** An interpretive report will be provided. Results will be characterized as positive, negative, or indeterminate for a clonal T-cell population. In the appropriate clinicopathologic setting, a monoclonal result is associated with a neoplastic proliferation of T cells (see Cautions).

**Reference Values:**
An interpretive report will be provided.
Positive, negative, or indeterminate for a clonal T-cell population


**TCP** 89319

**T-Cell Subsets, Naive, Memory and Activated**

**Clinical Information:** T cells, after completing development and initial differentiation in the thymus, enter the periphery as naive (n) T cells. Naive T cells undergo further differentiation into effector and memory T cells in the peripheral lymphoid organs after recognizing specific antigenic peptides in the context of major histocompatibility (MHC) molecules, through the antigen-specific T-cell receptor. In addition to the cognate signal of the peptide-MHC complex interaction (the term cognate refers to 2 biological molecules that normally interact), T cells require additional costimulatory signals to complete T-cell activation. Naive T cells circulate continuously through the lymph nodes and, on recognition of specific antigen, undergo activation. Due to their antigen-inexperienced state, naive T
cells require activation by more potent antigen-presenting cells, such as dendritic cells. Naive T cells can survive in circulation for prolonged periods of time and are very important in contributing to T-cell repertoire diversity. They proliferate in response to interleukin-2, as a consequence of their response to antigen through recognition of peptide-MHC costimulation. These expanded antigen-specific T cells undergo further differentiation into effector cells. The differentiation of naive CD8 T cells into cytotoxic effectors capable of killing target T cells loaded with endogenous peptides on MHC class I molecules may require additional costimulatory signals from CD4 T cells. Naive CD4 T cells also differentiate into different effector subsets such as Th1, Th2, and Th17, which produce specific cytokines. (1) T cells can be subdivided into naive and memory subsets based on the expression of cell-surface markers, such as CD45RA and CD45RO, among others. It was initially thought that the presence of cell-surface CD45RA indicated the naive subset, while the presence of CD45RO indicated memory subsets. But, it has now been shown that multiple, rather than single, markers are required to distinguish these subsets. (2) Lanzavecchia and Sallusto proposed a model where naive T cells expressing CD45RA and CCR7 lose CD45RA expression on recognition of antigen. (3) The surface markers for identifying naive T-cell subsets include CD45RA, CD62L (L-selectin), and CD27. (4, 5) Memory T cells are antigen-experienced cells that are present in greater numbers than antigen-specific precursors, and can respond more efficiently and rapidly to specific antigen. Memory T cells can maintain their populations independent of antigen by homeostatic proliferation in response to cytokines. While there are subcategories of memory T cells based on effector function and cell surface and cytolytic molecule expression, the 2 main categories of memory T cells are central memory T cells (Tcm) and effector memory T cells (Tem). (6, 7) Tcm express the CD45RO molecule along with CD62L (L-selectin) and CCR7, and are present mainly in lymphoid tissue. (6, 7) They are able to respond to antigen through rapid proliferation and expansion and differentiation into Tem. By themselves, Tcm are not directly effective in effector cytolytic function. Unlike Tcm, Tem express only CD45RO (not CD62L and CCR7). (6) As the name suggests, Tem have remarkable effector function, though they do not proliferate well. Tem are present throughout the circulation in peripheral tissues providing immune surveillance. Memory T cells are particularly important for maintenance of immune competence since they are associated with a rapid and effective response to pathogens. Therefore, depletion of this compartment has more immediate significance than the depletion of naive T cells. Activation of human T cells is critical for the optimal and appropriate performance of T-cell functions within the adaptive immune response. Activated naive T cells undergo proliferation, as well as subsequent differentiation into effector T cells, and are capable of producing cytokines that can modulate the immune response in a variety of ways. (8) There are several markers associated with T-cell activation, but those most commonly used include CD25 (IL-2R) (8) and MHC class II. (9) Additionally, the expression of the costimulatory molecule CD28 augments the T-cell activation response. (10) The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer cell counts, on the other hand, are constant throughout the day. (11) Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration. (12-14) In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells. (11) It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening (15), and during summer compared to winter. (16) These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

**Useful For:** Determining the presence of naive, memory, and activated T cells in various clinical contexts including autoimmune diseases, immunodeficiency states, T-cell recovery posthematopoietic stem cell transplant, DiGeorge syndrome, and as a measure for T-cell immune competence. Naive T-cells results can be used as a surrogate marker for thymic-derived T-cell reconstitution, when used in conjunction with assessment of T-cell receptor excision circles (TREC / T-Cell Receptor Excision Circles [TREC] Analysis for Immune Reconstitution) Assessing a patient’s relative risk for infections Evaluation of patients with cellular or combined primary immunodeficiencies Evaluation of T-cell reconstitution after hematopoietic stem cell transplant, chemotherapy, biological therapy, immunosuppression or immunomodulator therapy Evaluation of patients with autoimmune diseases Evaluation of HIV-positive patients for naive and memory subsets Evaluation of T-cell immune competence (presence of memory and activated T cells) in patients with recurrent infections.
**Interpretation:** Absence or reduction of naive T cells with or without T-cell lymphopenia indicates absent or impaired T-cell reconstitution or thymic output. Reduction in activated T cells can also indicate a reduced T-cell immune competent state. Increases in naive T cells with corresponding decreases in the memory T-cell compartment indicates a failure of further differentiation and effector function or selective loss of memory T cells and an increased risk for infection.

**Reference Values:**
The appropriate age-related reference values will be provided on the report.

**Clinical References:**

**T-Cell Subsets, Regulatory (Tregs)**

**Clinical Information:** Regulatory T cells (Tregs) are a population of CD4+ T cells with a unique role in the immune response. Tregs are crucial in suppressing aberrant pathological immune responses in autoimmune diseases, transplantation, and graft-vs-host disease after allogeneic hematopoietic stem cell transplantation. (1) Tregs are activated through the specific T-cell receptor, but their effector function is nonspecific and they regulate the local inflammatory response through cell-to-cell contact and cytokine secretion. (2) Tregs secrete interleukin (IL)-9 (IL-9), IL-10, and transforming growth factor-beta 1 (TGF-beta 1), which aid in the mediation of immunosuppressive activity. Chief characteristics of the Treg population are surface expression of the CD25 protein (IL-2Ra) and the intracellular presence of the transcription factor Foxp3. The IL-7 receptor (CD127) is downregulated on Foxp3+CD4+CD25+ T cells and provides an excellent alternative cell-surface marker to Foxp3 for detecting natural Tregs (CD4+CD25+CD127lo). (2) Natural Tregs account for 5% to 10% of the total CD4 T-cell population and are derived from thymic precursors. (3) Since CD25 is also expressed on activated T cells, the concomitant use of CD127 permits the differentiation of Tregs from activated T cells. (4) Natural Tregs express the memory marker CD45RO and have limited ability to proliferate.
However, within the CD4+CD25+Treg population, there is a subset of Tregs that express the CD45 isoform generally associated with naive T cells (CD45RA), and this subset has been called natural naive (Nn) Tregs. Nn Tregs are most prominent in young adults and decrease with age along with the rest of the naive CD4 T-cell population. Like other naive T cells, Nn Tregs have high proliferative capacity, as well as the suppressor activity of other Treg subsets. Present evidence suggests that Nn Tregs also have a thymic ancestry and are the precursors of the natural Tregs (that are of the memory, antigen-experienced phenotype) and appear to be composed of T cells with self-reactive T-cell receptors. Other subsets of Tregs include the Th3 cells, which secrete high levels of TGF-beta 1 and can be induced by oral administration of antigen, and regulatory T class 1 (Tr1) cells, which secrete interferon-gamma and IL-10. These Treg subsets are most likely induced in the periphery and are responsible for peripheral tolerance to self antigens. The suppressive activity of Th3 and Tr1 cells are related to the cytokines they produce, TGF-beta 1 and IL-10, respectively. The absence of Tregs as a result of mutations in the FOXP3 gene cause a primary immunodeficiency called IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked inheritance). Patients with IPEX have a complex manifestation of symptoms including severe watery diarrhea due to significant villous atrophy and lymphocytic infiltration of bowel mucosa, early-onset autoimmune endocrinopathies involving the pancreas or thyroid, and a dermatitic (eczematous) rash. In addition, there are other autoimmune manifestations including autoimmune cytopenias and autoimmune hepatitis. Renal disease is quite common in these patients. Finally, these patients also have a significant predisposition to infections including sepsis, pneumonia, meningitis, and osteomyelitis. Decreased Foxp3+CD4+CD25+Tregs have been reported in 1 patient with a STAT5b mutation. There is an expansion of Nn Tregs in patients with monoclonal gammopathy of undetermined significance and multiple myeloma, likely as a response to the process of malignant transformation. Expansion of Tregs has also been reported in other neoplasias including B-cell chronic lymphocytic leukemia, Hodgkin disease, and solid tumors. The absolute counts of lymphocyte subsets are known to be influenced by a variety of biological factors, including hormones, the environment, and temperature. The studies on diurnal (circadian) variation in lymphocyte counts have demonstrated progressive increase in CD4 T-cell count throughout the day, while CD8 T cells and CD19+ B cells increase between 8:30 am and noon, with no change between noon and afternoon. Natural killer cell counts, on the other hand, are constant throughout the day. Circadian variations in circulating T-cell counts have been shown to be negatively correlated with plasma cortisol concentration. In fact, cortisol and catecholamine concentrations control distribution and, therefore, numbers of naive versus effector CD4 and CD8 T cells. It is generally accepted that lower CD4 T-cell counts are seen in the morning compared with the evening, and during summer compared to winter. These data, therefore, indicate that timing and consistency in timing of blood collection is critical when serially monitoring patients for lymphocyte subsets.

**Useful For:** Evaluating patients with clinical features of IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked inheritance) and other primary immunodeficiencies, autoimmune diseases, allergy and asthma, and graft-vs-host disease post-hematopoietic stem cell transplantation

**Interpretation:** The lack of regulatory T (Treg) cells is associated with mutations in the FOXP3 gene. Low Tregs are also seen in the context of STAT5b mutations. Reduced Nn Tregs and natural Tregs are likely to predispose to autoimmunity, while reductions in Th3/Tr1 cells may impair oral and peripheral tolerance, also facilitating the development of autoimmunity. The presence of expanded naive Tregs may indicate a process of malignant transformation, if other clinical features of malignant disease are present. Increased Tregs in donor stem cell allografts have been associated with a reduced incidence of graft-versus-host disease (ie, mediating a protective effect) after allogeneic stem cell transplantation.

**Reference Values:** The appropriate age-related reference values will be provided on the report.

**Clinical References:**

**TLBLF 65413**

**T-Lymphoblastic Leukemia/Lymphoma, FISH, Tissue**

**Clinical Information:** T-lymphoblastic lymphoma (T-LBL) is the non-leukemic form of T-acute lymphoblastic leukemia (T-ALL). In the United States, the incidence of ALL is roughly 6,000 new cases per year (as of 2009), or approximately 1 in 50,000. ALL accounts for approximately 70 percent of all childhood leukemia cases (ages 0 to 19 years), making it the most common type of childhood cancer. Approximately 85% of pediatric ALL cases are B-cell lineage (B-ALL) and 15% are T-cell lineage (T-ALL). T-ALL is more common in adolescents than younger children and accounts for 25% of adult ALL. When occurring as a primary lymphoblastic lymphoma, approximately 90% are T-cell lineage versus only 10% B-cell lineage. T-LBL characteristically presents in adolescents and young adults as a mediastinal mass with or without concurrent bone marrow involvement. It is not uncommon that the only sample available with T-LBL involvement is a paraffin-embedded mediastinal or lymph node biopsy specimen. Specific genetic abnormalities can be identified in the majority of T-ALL/LBL cases, although many of the classic abnormalities are “cryptic” by conventional chromosome studies and must be identified by fluorescence in situ hybridization (FISH) studies. Each of the genetic subgroups are important to detect and can be critical prognostic markers. One predictive marker, amplification of the ABL1 gene region, has been identified in 5% of T-ALL, and these patients may be responsive to targeted tyrosine kinase inhibitors. A combination of cytogenetic and FISH testing is currently recommended in all pediatric and adult patients to characterize the T-ALL/LBL clone for prognostic genetic subgroups.

**Useful For:** Detecting a neoplastic clone associated with the common chromosome abnormalities seen in patients with T-cell lymphoblastic leukemia or lymphoma

**Interpretation:** A positive result is detected when the percent of cells with an abnormality exceeds the normal cutoff for the probe set. A positive result is not diagnostic for T-lymphoblastic lymphoma (T-LBL), but may provide relevant prognostic information. The absence of an abnormal clone does not rule out the presence of neoplastic disorder.

**Reference Values:**
An interpretive report will be provided.

T3 (Triiodothyronine), Free, Serum

**Clinical Information:** Normally triiodothyronine (T3) circulates tightly bound to thyroxine-binding globulin and albumin. Only 0.3% of the total T3 is unbound (free); the free fraction is the active form. In hyperthyroidism, both thyroxine (tetraiodothyronine; thyroxine: T4) and T3 levels (total and free) are usually elevated, but in a small subset of hyperthyroid patients (T3 toxicosis) only T3 is elevated. Generally, free T3 (FT3) measurement is not necessary since total T3 will suffice. However, FT3 levels may be required to evaluate clinically euthyroid patients who have an altered distribution of binding proteins (eg, pregnancy, dysalbuminemia). Some investigators recommend the FT3 assay for monitoring thyroid replacement therapy, although its clinical role is not precisely defined.

**Useful For:** Free triiodothyronine (T3) is a second- or third-level test of thyroid function; it provides further confirmation of hyperthyroidism, supplementing the tetraiodothyronine (T4), sensitive thyrotropin (sTSH), and total T3 assays Evaluating clinically euthyroid patients who have an altered distribution of binding proteins Monitoring thyroid hormone replacement therapy

**Interpretation:** Elevated free triiodothyronine (FT3) values are associated with thyrotoxicosis or excess thyroid hormone replacement.

**Reference Values:**
> or =1 year: 2.8-4.4 pg/mL

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.


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T3 (Triiodothyronine), Reverse, Serum

**Clinical Information:** Reverse triiodothyronine (rT3) differs from triiodothyronine (T3) in the positions of the iodine atoms attached to the aromatic rings. The majority of rT3 found in the circulation is formed by peripheral deiodination (removal of an iodine atom) of T4 (thyroxine). rT3 is believed to be metabolically inactive. The rT3 level tends to follow the T4 level: low in hypothyroidism and high in hyperthyroidism. Additionally, increased levels of rT3 have been observed in starvation, anorexia nervosa, severe trauma and hemorrhagic shock, hepatic dysfunction, postoperative states, severe infection, and in burn patients (ie, "sick euthyroid" syndrome). This appears to be the result of a switchover in deiodination functions with the conversion of T4 to rT3 being favored over the production of T3.

**Useful For:** An aid in the diagnosis of the "sick euthyroid" syndrome

**Interpretation:** In hospitalized or sick patients with low triiodothyronine (T3) values, elevated reverse triiodothyronine (rT3) values are consistent with "sick euthyroid" syndrome. Also, the finding on an elevated rT3 level in a critically ill patient helps exclude a diagnosis of hypothyroidism. The rT3 is high in patients on medications such as propylthiouracil, ipodate, propranolol, amiodarone, dexamethasone, and the anesthetic agent halothane. Dilantin decreases rT3 due to the displacement from thyroxine-binding globulin, which causes increased rT3 clearance. To convert from ng/dL to nmol/L, multiply the ng/dL result by 0.01536.

**Reference Values:**
10-24 ng/dL

**Clinical References:** Moore WT, Eastman RC: Diagnostic Endocrinology. St. Louis, Mosby, 1990,
### T3 (Triiodothyronine), Total, Serum

**Clinical Information:** Thyroid hormones regulate a number of developmental, metabolic, and neural activities throughout the body. The thyroid gland synthesizes 2 hormones. The 2 main hormones secreted by the thyroid gland are thyroxine, which contains 4 atoms of iodine (T4), and triiodothyronine (T3). T3 production in the thyroid gland constitutes approximately 20% of the total T3; the rest is generated by the conversion (deiodination) of T4 to T3 is also produced by conversion (deiodination) of T4 in peripheral tissues. Circulating levels of T4 are much greater than T3 levels, but T3 is biologically the most metabolically active hormone (3-4 times more potent than T4) although its effect is briefer due to its shorter half-life compared to T4. Thyroid hormones circulate primarily bound to carrier proteins (eg, thyroid-binding globulin: TBG, prealbumin, and albumin); whereas only a small fraction circulates unbound (free). Only the free forms are metabolically active. While both T3 and T4 are bound to TBG, T3 is bound less firmly than T4. Total T3 consists of both the bound and unbound fractions. In hyperthyroidism, both T4 and T3 levels are usually elevated, but in a small subset of hyperthyroid patients only T3 is elevated (T3 toxicosis). In hypothyroidism T4 and T3 levels are decreased. T3 levels are frequently low in sick or hospitalized euthyroid patients. See Thyroid Function Ordering Algorithm in Special Instructions.

**Useful For:** Second-order testing for hyperthyroidism in patients with low thyroid-stimulating hormone values and normal thyroxine levels Diagnosis of triiodothyronine toxicosis

**Interpretation:** Triiodothyronine (T3) values >200 ng/dL in adults or > age related cutoffs in children are consistent with hyperthyroidism or increased thyroid hormone-binding proteins. Abnormal levels (high or low) of thyroid hormone-binding proteins (primarily albumin and thyroid-binding globulin) may cause abnormal T3 concentrations in euthyroid patients.

**Reference Values:**

- Pediatric
  - 0-5 days: 73-288 ng/dL
  - 6 days-2 months: 80-275 ng/dL
  - 3-11 months: 86-265 ng/dL
  - 1-5 years: 92-248 ng/dL
  - 6-10 years: 93-231 ng/dL
  - 11-19 years: 91-218 ng/dL

- Adult (> or =20 years): 80-200 ng/dL

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.

**Clinical References:**

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### T4 (Thyroxine), Free by Dialysis, Serum

**Clinical Information:** Thyroxine (T4) and triiodothyronine (T3) are the 2 biologically active thyroid hormones. T4 makes up more than 80% of circulating thyroid hormones. Following secretion by the thyroid gland, approximately 70% of circulating T4 and T3 are bound to thyroid-binding globulin (TBG), while 10% to 20% each are bound to transthyretin (TTR) and albumin, respectively. Less than 0.1% circulates as free T4 (FT4) or free T3 (FT3). FT4 and FT3 enter and leave cells freely by diffusion. Only the free hormones are biologically active, but bound and free fractions are in equilibrium. Equilibrium with TTR and albumin is rapid. By contrast, TBG binds thyroid hormones very tightly and equilibrium dissociation is slow. Biologically, TBG-bound thyroid hormone serves as a
hormone reservoir and T4 serves as a prohormone for T3. Within cells, T4 is either converted to T3, which is about 5 times as potent as T4, or reverse T3, which is biologically inactive. Ultimately, T3, and to a much lesser degree T4, bind to the nuclear thyroid hormone receptor, altering gene expression patterns in a tissue-specific fashion. Under normal physiologic conditions, FT4 and FT3 exert direct and indirect negative feedback on pituitary thyrotropin (thyroid-stimulating hormone: TSH) levels, the major hormone regulating thyroid gland activity. This results in tight regulation of thyroid hormone production and constant levels of FT4 and FT3 independent of the binding protein concentration. Measurement of FT4 and FT3, in conjunction with TSH measurement, therefore represents the best method to determine thyroid function status. It also allows determination of whether hyperthyroidism (increased FT4) or hypothyroidism (low FT4) are primary (the majority of cases, TSH altered in the opposite direction as FT4) or secondary/tertiary (hypothalamic/pituitary origin, TSH altered in the same direction as FT4). By contrast, total T4 and T3 levels can vary widely as a response to changes in binding protein levels, without any change in free thyroid hormone levels and, hence, actual thyroid function status. FT4 is usually measured by automated analog immunoassays. In most instances, this will result in accurate results. However, abnormal types or quantities of binding proteins found in some patients and most often related to other illnesses or drug treatments, may interfere in the accurate measurement of FT4 by analog immunoassays. These problems can be overcome by measuring FT4 by equilibrium dialysis, free from interfering proteins.

**Useful For:** Determining thyroid status of sick, hospitalized patients Determining thyroid status of patients in whom abnormal binding proteins have been identified Possibly useful in pediatric patients

**Interpretation:** All free hormone assays should be combined with thyroid-stimulating hormone measurements. Free thyroxine (FT4) levels below 0.8 ng/dL indicate possible hypothyroidism. FT4 levels above 2.0 ng/dL indicates possible hyperthyroidism. Neonates can have significantly higher FT4 levels. The hypothalamic-pituitary-thyroid axis can take several days or, sometimes, weeks to mature.

**Reference Values:**
0.8-2.0 ng/dL
Reference values apply to all ages.

**Clinical References:**

**FRT4**

**T4 (Thyroxine), Free, Serum**

**Clinical Information:** Free thyroxine (FT4) comprises a small fraction of total thyroxine. The FT4 is available to the tissues and is, therefore, the metabolically active fraction. Elevations in FT4 cause hyperthyroidism, while decreases cause hypothyroidism.

**Useful For:** Evaluation of suspected thyroid function disorders using free thyroxine measured together with thyroid-stimulating hormone

**Interpretation:** Elevated values suggest hyperthyroidism or exogenous thyroxine. Decreased values suggest hypothyroidism. Free thyroxine (FT4) works well to correct total T4 values for thyroxine-binding globulin alterations, but may give misleading values when abnormal binding proteins are present or the patient has other major illnesses (euthyroid sick syndrome).

**Reference Values:**

<table>
<thead>
<tr>
<th>Pediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 days: 0.9-2.5 ng/dL</td>
</tr>
<tr>
<td>6 days-2 months: 0.9-2.2 ng/dL</td>
</tr>
<tr>
<td>3-11 months: 0.9-2.0 ng/dL</td>
</tr>
<tr>
<td>1-5 years: 1.0-1.8 ng/dL</td>
</tr>
<tr>
<td>6-10 years: 1.0-1.7 ng/dL</td>
</tr>
</tbody>
</table>
### T4 (Thyroxine), Total and Free

**Clinical Information:** Thyroxine (T4), TOTAL: T4 is synthesized in the thyroid gland. T4 is metabolized to T3 peripherally by deiodination. T4 is considered a reservoir or prohormone for T3, the biologically most active thyroid hormone. About 0.05% of circulating T4 is in the free or unbound portion. The remainder is bound to thyroxine-binding globulin (TBG), prealbumin, and albumin. The hypothalamus secretes thyrotropin-releasing hormone (TRH), which stimulates the pituitary to release thyroid-stimulating hormone (TSH). TSH stimulates the thyroid to secrete T4. T4 is partially converted peripherally to triiodothyronine (T3). High amounts of T4 and T3 (mostly from peripheral conversion of T4) cause hyperthyroidism. T4 and T3 cause positive feedback to the pituitary and hypothalamus with resultant suppression or stimulation of the thyroid gland as follows: decrease of TSH if T3 or T4 is high (hyperthyroidism), and increase of TSH if T3 or T4 is low (hypothyroidism). Measurement of total T4 gives a reliable reflection of clinical thyroid status in the absence of protein binding abnormalities. However, changes in binding proteins can occur which affect the level of total T4 but leave the level of unbound hormone unchanged. THYROXINE (T4), FREE: Free thyroxine comprises a small fraction of total thyroxine. The free T4 (FT4) is available to the tissues and is, therefore, the metabolically active fraction. Elevations in FT4 cause hyperthyroidism, while decreases cause hypothyroidism.

**Useful For:** Thyroxine (T4) and free T4 are measured together with thyroid-stimulating hormone when thyroid function disorders are suspected.

**Reference Values:**

**T4 (THYROXINE), TOTAL ONLY**
- Adult (> or =20 years): 4.5-11.7 mcg/dL
- Pediatric:
  - 0-5 days: 5.0-18.5 mcg/dL
  - 6 days-2 months: 5.4-17.0 mcg/dL
  - 3-11 months: 5.7-16.0 mcg/dL
  - 1-5 years: 6.0-14.7 mcg/dL
  - 6-10 years: 6.0-13.8 mcg/dL
  - 11-19 years: 5.9-13.2 mcg/dL

**T4 (THYROXINE), FREE**
- Adult (> or =20 years of age): 0.9-1.7 ng/dL
- 0-5 days: 0.9-2.5 ng/dL
- 6 days-2 months: 0.9-2.2 ng/dL
- 3-11 months: 0.9-2.0 ng/dL
- 1-5 years: 1.0-1.8 ng/dL
- 6-10 years: 1.0-1.7 ng/dL
- 11-19 years: 1.0-1.6 ng/dL

triiodothyronine (T3) peripherally by deiodination. T4 is considered a reservoir or prohormone for T3, the biologically most active thyroid hormone. About 0.05% of circulating T4 is in the free or unbound portion. The remainder is bound to thyroxine-binding globulin (TBG), prealbumin, and albumin. The hypothalamus secretes thyrotropin-releasing hormone (TRH), which stimulates the pituitary to release thyroid-stimulating hormone (TSH). TSH stimulates the thyroid to secrete T4. T4 is partially converted peripherally to T3. High amounts of T4 and T3 (mostly from peripheral conversion of T4) cause hyperthyroidism. T4 and T3 cause positive feedback to the pituitary and hypothalamus with resultant suppression or stimulation of the thyroid gland as follows: decrease of TSH if T3 or T4 is high (hyperthyroidism), and increase of TSH if T3 or T4 is low (hypothyroidism). Measurement of total T4 gives a reliable reflection of clinical thyroid status in the absence of protein-binding abnormalities and nonthyroidal illness. However, changes in binding proteins can occur that affect the level of total T4, but leave the level of unbound hormone unchanged. See Thyroid Function Ordering Algorithm in Special Instructions.

Useful For: Monitoring treatment with synthetic hormones (synthetic triiodothyronine will cause a low total thyroxine: T4) Monitoring treatment of hyperthyroidism with thiouracil and other antithyroid drugs

Interpretation: Values of more than 11.7 mcg/dL in adults or more than the age-related cutoffs in children are seen in hyperthyroidism and patients with acute thyroiditis. Values below 4.5 mcg/dL in adults or below the age-related cutoffs in children are seen in hypothyroidism, myxedema, cretinism, chronic thyroiditis, and occasionally, subacute thyroiditis. Increased total thyroxine (T4) is seen in pregnancy and patients who are on estrogen medication. These patients have increased total T4 levels (increased thyroxine-binding globulin: TBG levels). Decreased total T4 is seen in patients on treatment with anabolic steroids, or nephrosis (decreased TBG levels). A thyrotropin-releasing hormone stimulation test may be required for certain cases of hyperthyroidism. Clinical findings are necessary to determine if thyroid-stimulating hormone, TBG, or free T4 testing is needed.

Reference Values:

Pediatric
0-5 days: 5.0-18.5 mcg/dL
6 days-2 months: 5.4-17.0 mcg/dL
3-11 months: 5.7-16.0 mcg/dL
1-5 years: 6.0-14.7 mcg/dL
6-10 years: 6.0-13.8 mcg/dL
11-19 years: 5.9-13.2 mcg/dL

Adult (> or =20 years): 4.5-11.7 mcg/dL

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.


TAKRO

Tacrolimus, Blood

Clinical Information: Tacrolimus is a macrolide antibiotic derived from the fungus Streptomyces tsukubaensis. Like cyclosporine, tacrolimus inhibits calcineurin to suppress T cells. Tacrolimus is metabolized by CYP3A4, thus its concentrations are affected by drugs that inhibit (calcium channel blockers, antifungal agents, some antibiotics, grapefruit juice) or induce (anticonvulsants, rifampin) this enzyme. Tacrolimus has a narrow therapeutic range, and adverse effects are common, particularly at high dose and concentrations, making therapeutic drug monitoring essential. Since 90% of tacrolimus is in the cellular components of blood, especially erythrocytes, whole blood is the preferred specimen for analysis of trough concentrations. Target steady-state concentrations vary depending on clinical protocol, the presence or risk of rejection, time from transplant, type of allograft, concomitant immunosuppression, and side effects (mainly nephrotoxicity). Optimal trough blood concentrations are generally between 5.0 and 15.0 ng/mL. Higher levels are often sought immediately after transplant, but as organ function stabilizes at about 4 weeks from transplant, doses are generally reduced in stable patients for most solid organ transplants.
transplants. Trough concentrations should be maintained below 20 ng/mL.

**Useful For:** Monitoring whole blood tacrolimus concentration during therapy, particularly in individuals coadministered CYP3A4 substrates, inhibitors, or inducers Adjusting dose to optimize immunosuppression while minimizing toxicity Evaluating patient compliance

**Interpretation:** Most individuals display optimal response to tacrolimus with trough whole blood levels of 5.0 to 15.0 ng/mL. Preferred therapeutic ranges may vary by transplant type, protocol, and comediations. Therapeutic ranges are based on samples drawn at trough (ie, immediately before a scheduled dose). Blood drawn at other times will yield higher results. The assay is specific for tacrolimus; it does not cross-react with cyclosporine, cyclosporine metabolites, sirolimus, sirolimus metabolites, or tacrolimus metabolites. Results by liquid chromatography with detection by tandem mass spectrometry are approximately 30% less than by immunoassay.

**Reference Values:**
5.0-15.0 ng/mL (Trough)

Target steady-state trough concentrations vary depending on the type of transplant, concomitant immunosuppression, clinical/institutional protocols, and time post-transplant. Results should be interpreted in conjunction with this clinical information and any physical signs/symptoms of rejection/toxicity.


**Tacrolimus, Peak, Blood**

**Clinical Information:** Tacrolimus (Prograf) is a macrolide antibiotic derived from the fungus Streptomyces tsukubaensis. Like cyclosporine, tacrolimus inhibits calcineurin to suppress T cells. Tacrolimus is metabolized by CYP3A4; thus, its concentration is affected by drugs that inhibit (calcium channel blockers, antifungal agents, some antibiotics, grapefruit juice) or induce (anticonvulsants, rifampin) this enzyme. Tacrolimus has a narrow therapeutic range and adverse effects are common, particularly at high dose and concentrations, making therapeutic drug monitoring essential. Since 90% of tacrolimus is in the cellular components of blood, especially erythrocytes, whole blood is the preferred specimen for analysis of trough concentrations. Target steady-state concentrations vary depending on clinical protocol, the presence or risk of rejection, time from transplant, type of allograft, concomitant immunosuppression, and side effects (mainly nephrotoxicity). Optimal trough blood concentrations are generally between 5.0 and 15.0 ng/mL. Higher levels are often sought immediately after transplant, but as organ function stabilizes at about 4 weeks from transplant, doses are generally reduced in solid organ transplant patients who are stable. Trough concentrations should be maintained below 20 ng/mL. Optimal postdose sampling strategies and blood concentrations have not been well established for tacrolimus. A study of 54 liver transplant patients suggested that most individuals have tacrolimus blood concentrations ranging between 5.0 and 30.0 ng/mL in samples drawn 1 to 4 hours after dosing, although some patients showed slightly higher blood concentrations at 1-hour postdose.

**Useful For:** Assessment of postdosing (peak) blood tacrolimus concentrations

**Interpretation:** This test measures postdose levels of tacrolimus. Established reference ranges reflect trough measurement, and are not applicable to samples drawn after dosing. No reference ranges or standard sampling protocols have been established for postdosing tacrolimus levels, but a limited study of liver transplant recipients suggests most patients will show postdose tacrolimus levels ranging from 5.0 to 30.0 ng/mL when drawn 1 to 4 hours after dosing. The narrow therapeutic window and high individual pharmacokinetic variability of tacrolimus make regulation of dose by blood concentrations essential. Since 90% of the drug is in the cellular components of blood, especially erythrocytes, whole blood, rather than plasma, concentrations are measured and correlate better with efficacy and toxicity. This assay is specific for tacrolimus; it does not cross-react with cyclosporine, cyclosporine metabolites,
sirolimus, sirolimus metabolites, or tacrolimus metabolites. Results by liquid chromatography with detection by tandem mass spectrometry (LC-MS/MS) are approximately 30% less than by immunoassay.

**Reference Values:**
5.0-30.0 ng/mL

Target steady-state trough concentrations vary depending on the type of transplant, concomitant immunosuppression, clinical/institutional protocols, and time posttransplant. Results should be interpreted in conjunction with this clinical information and any physical signs or symptoms of rejection or toxicity.


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**Tapentadol and Metabolite, Random Urine**

**Clinical Information:** Tapentadol, a centrally acting opioid analgesic, is used in the treatment of moderate to severe acute and chronic pain and for the management of neuropathic pain associated with diabetic peripheral neuropathy in adults (extended release formulation only). Tapentadol acts as an opiate agonist through its binding to mu-opioid receptors and through the inhibition of norepinephrine reuptake. About 97% of the parent drug is metabolized. The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. Tapentadol and its metabolites (N-desmethyltapentadol and hydroxyl-tapentadol) are excreted almost exclusively via the kidneys and approximately 70% of the drug is excreted in urine in the conjugated form. The metabolites of tapentadol have no analgesic activity. The half-life of tapentadol is approximately 4 hours. Opioid analgesics have high abuse potential and the regular use of tapentadol may result in physical dependence and tolerance. Tapentadol is a schedule II controlled substance with abuse liability similar to other opioid agonists.

**Useful For:** Monitoring of compliance utilizing tapentadol Detection and confirmation of the illicit use of tapentadol

**Interpretation:** The presence of tapentadol or N-desmethyltapentadol levels of 25 ng/mL or higher is a strong indicator that the patient has used tapentadol.

**Reference Values:**
Cutoff: 25 ng/mL

Note: Tapentadol concentrations will be reported quantitatively and N-desmethyltapentadol will be reported qualitatively (Present or Negative).


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**Tapioca IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L
**Targeted Opioid Screen, Urine**

**Clinical Information:** Opioids are a large class of medications commonly used to relieve acute and chronic pain or help manage opioid abuse and dependence. Medications that fall into this class include: buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, tapentadol, tramadol, and others. Opioids work by binding to the opioid receptors that are found in the brain, spinal cord, gastrointestinal tract, and other organs. Common side effects include drowsiness, confusion, nausea, constipation, and in severe cases respiratory depression depending on the dose. These medications can also produce physical and psychological dependence and have a high risk for abuse and diversion, which is one of the main reasons many professional practice guidelines recommend compliance testing in patients prescribed these medications. Opioids are readily absorbed from the gastrointestinal tract, nasal mucosa, lungs, and after subcutaneous or intramuscular injection. Opioids are primarily excreted from the kidney in both free and conjugated forms. This assay doesn’t hydrolyze the urine sample and looks for both parent drugs and metabolites (including glucuronide forms). The detection window for most opioids in urine is approximately 1 to 3 days with longer detection times for some compounds (i.e., methadone).

**Useful For:** This high-resolution accurate mass method qualitatively (present vs. not detected) identifies 33 opioid compounds (parent drug and metabolites) in urine to help determine compliance or identify illicit opioid drug use.

**Interpretation:** If an opioid or its corresponding metabolites are identified (present), it indicates that the patient has used the respective opioids in the recent past. The absence of expected opioids or their metabolites may indicate noncompliance, inappropriate timing of specimen collection relative to drug administration, poor drug absorption, diluted or adulterated urine, or limitations of testing. The concentration of the drug must be greater than or equal to the cutoff to be reported as present. If a specific drug concentration is required, the laboratory must be contacted within 2 weeks of specimen collection/testing to request quantification by a second analytical technique at an additional charge.

**Reference Values:**

Not Detected

Cutoff concentrations:
- Codeine: 25 ng/mL
- Codeine-6-beta-glucuronide: 100 ng/mL
- Morphine: 25 ng/mL
- Morphine-6-beta-glucuronide: 100 ng/mL
- 6-monoacetylmorphine: 25 ng/mL
- Hydrocodone: 25 ng/mL
- Norhydrocodone: 25 ng/mL
- Dihydrocodeine: 25 ng/mL
- Hydromorphone: 25 ng/mL
- Hydromorphone-3-beta-glucuronide: 100 ng/mL
- Oxycodone: 25 ng/mL
- Noroxycodone: 25 ng/mL
- Oxymorphone: 25 ng/mL
- Oxymorphone-3-beta-glucuronide: 100 ng/mL
- Noroxymorphone: 25 ng/mL
- Fentanyl: 2 ng/mL
- Norfentanyl: 2 ng/mL
- Meperidine: 25 ng/mL
- Normeperidine: 25 ng/mL
- Naloxone: 25 ng/mL
- Naloxone-3-beta-glucuronide: 100 ng/mL
- Methadone: 25 ng/mL
- EDDP: 25 ng/mL
- Propoxyphene: 25 ng/mL
- Norpropoxyphene: 25 ng/mL
Tramadol: 25 ng/mL
O-desmethyltramadol: 25 ng/mL
Tapentadol: 25 ng/mL
N-desmethyltapentadol: 50 ng/mL
Tapentadol-beta-glucuronide: 100 ng/mL
Buprenorphine: 5 ng/mL
Norbuprenorphine: 5 ng/mL
Norbuprenorphine glucuronide: 20 ng/mL


Tarragon, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

Clinical References: Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and
Tartrate-Resistant Acid Phosphatase (TRAP) Immunostain, Technical Component Only

**Clinical Information:** Tartrate-resistant acid phosphatase (TRAP) is a basic, iron-binding protein found within the cytoplasmic granules of cells of hairy cell leukemia. TRAP can be useful in distinguishing hairy cell leukemia from other types of B-cell lymphomas. Caution should be used since other types of lymphoma can also be positive, such as marginal zone lymphoma, but usually their staining is less intense. Normal mast cells also express TRAP.

**Useful For:** Classification of leukemias and lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

TAU3

TAU 3 Immunostain, Technical Component Only

**Clinical Information:** The Tau 3 antibody stains microtubule-associated proteins in the brain that are associated with diseases of the central nervous system, especially neurodegenerative disorders

**Useful For:** Diagnosis of neurodegenerative disorders

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

TAU 4 Immunostain, Technical Component Only

Clinical Information: The Tau 4 antibody stains microtubule-associated proteins in the brain that are associated with diseases of the central nervous system, especially neurodegenerative disorders.

Useful For: Diagnosis of neurodegenerative disorders

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


TAU Immunostain, Technical Component Only

Clinical Information: Tau proteins are microtubule-associated proteins that regulate the dynamics of the microtubule network, and are especially involved in the axonal transport and neuronal plasticity. Antibodies to Tau proteins stain the tangles of microtubules associated with Alzheimer cytoskeletal pathology; neurofibrillary tangles, neuropil threads, and neuritic ("senile") plaques (NPs). Tau has become important in the analysis of a wide variety of neurodegenerative disorders, including Alzheimer disease, Pick disease, corticobasal degeneration, supranuclear palsy, multisystem atrophy, as well as a recently recognized category of disorders known as tauopathies.

Useful For: Analysis of neurodegenerative disorders

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Tay-Sachs Disease, HEXA Gene, Full Gene Analysis

Clinical Information: Tay-Sachs disease (TSD) is an inherited lysosomal storage disease caused by a deficiency of the enzyme beta-hexosaminidase A. It is characterized by accumulation of GM2 gangliosides in cells of the brain and central nervous system. The HEXA gene encodes the alpha subunit of beta-hexosaminidase A and mutations in this gene cause TSD. TSD occurs in approximately 1 in 200,000 live births with a carrier frequency of 1 in 250 to 1 in 300 in the general population. The carrier frequency for this disease in individuals of Ashkenazi Jewish ancestry is 1 in 31. The classic form of TSD becomes apparent in infancy when mild motor weakness is noted along with impaired visual acuity and the presence of a "startle response." Other manifestations include progressive neurodegeneration, seizures, and blindness, leading to total incapacitation and death. The subacute and adult-onset types of TSD are characterized by later ages of onset and a broad spectrum of disease symptoms and severity. TSD is inherited in an autosomal recessive manner. Several common mutations in the HEXA gene account for 92% of disease-causing mutations in the Ashkenazi Jewish population. Testing for these mutations is available as a panel, TSDP / Tay-Sachs Disease, Mutation Analysis, HEXA. In non-Ashkenazi Jewish individuals, the detection rate for the common mutations is significantly decreased. Sequencing of the entire HEXA gene detects less common disease-causing mutations. The recommended first-tier test for TSD carrier screening and diagnosis in all patients is a biochemical test that measures hexosaminidase A activity in white blood cells, NAGW / Hexosaminidase A and Total Hexosaminidase, Leukocytes.

Useful For: Second-tier test for confirming a biochemical diagnosis of Tay-Sachs disease (TSD) Carrier testing of individuals with a family history of TSD but an affected individual is not available for testing or disease-causing mutations have not been identified Testing individuals with enzyme activity consistent with carrier status but negative molecular testing by a panel of common mutations

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values: An interpretive report will be provided.


Tay-Sachs Disease, Mutation Analysis, HEXA

Clinical Information: Tay-Sachs disease is caused by an absence of hexosaminidase (Hex A) enzyme activity, which results in the accumulation of the sphingolipid GM2 ganglioside. Mutations within the alpha subunit of the hexosaminidase A gene, HEXA, cause the clinical manifestations associated with Tay-Sachs disease (TSD). The classic form of TSD becomes apparent in infancy when mild motor weakness is noted along with impaired visual acuity and the presence of a "startle response." Other manifestations of this condition include progressive neurodegeneration, seizures, and blindness leading to total incapacitation and death. Other types of TSD (eg, subacute and adult onset) are characterized by later ages of onset and death. The symptoms and severity of disease vary widely. TSD is inherited in an autosomal recessive manner. The carrier frequency for TSD disease in the Ashkenazi Jewish population is 1/31. This panel tests for the 3 common mutations in the Ashkenazi Jewish population: 1278insTATC, G269S, and IVS12+1G->C. When performed in conjunction with hexosaminidase A biochemical testing, the mutation detection rate using this assay is approximately 99%. Also included in this analysis are the mutations IVS9+1G->A and 7.6 kb, del 5'UTR-IVS+1 that
are over-represented in individuals of Celtic or French Canadian ancestry, respectively. A common cause of false-positive carrier screening by enzyme analysis, particularly among individuals of non-Ashkenazi Jewish descent, is due to the presence of a pseudodeficiency allele, either R247W or R249W. These sequence variations are not associated with disease, but result in the production of a hexosaminidase A enzyme with decreased activity towards the artificial substrate used in the enzyme assay. Both pseudodeficiency alleles are evaluated for by this panel. The recommended first-tier test to screen for TSD is biochemical analysis measuring hexosaminidase enzyme activity. NAGW / Hexosaminidase A and Total Hexosaminidase, Leukocytes. Molecular tests form the basis of confirmatory diagnostic or carrier testing. See Tay-Sachs Disease Carrier Testing Protocol in Special Instructions for additional information. Alternatively, full gene sequencing is available to evaluate for mutations in all coding regions and exon/intron boundaries of the HEXA gene by ordering HEXAZ / Tay-Sachs Disease, HEXA Gene, Full Gene Analysis.

Useful For: Carrier testing of individuals of Ashkenazi Jewish ancestry or who have a family history of Tay-Sachs disease Determining Tay-Sachs disease carrier status for individuals with enzyme activity within the carrier or equivocal ranges Prenatal diagnosis of Tay-Sachs disease for at-risk families Confirmation of suspected clinical diagnosis of Tay-Sachs disease in individuals of Ashkenazi Jewish ancestry

Interpretation: An interpretive report will be provided.

Reference Values: An interpretive report will be provided.


TCRB V-Beta Repertoire Analysis by Spectratyping, Blood

Clinical Information: The rearrangement of the T-cell receptor (TCR) through somatic recombination of V (variable), D (diversity), J (joining), and C (constant) regions is a defining event in the development and maturation of a T cell. TCR gene rearrangement takes place in the thymus. During the process of rearrangement, DNA byproducts are generated called T-cell receptor excision circles (TRECs) and these are used as markers of T cells that have recently emigrated from the thymus (TREC / T-Cell Receptor Excision Circles (TREC) Analysis, Blood). T cells, as part of the adaptive immune system, recognize foreign antigens when they are displayed on the surface of the body's own cells. T cells recognize these foreign antigens as peptides presented in the context of major histocompatibility complex (MHC) molecules through their T-cell receptors. Each TCR exists as 2 different polypeptide chains (heterodimers) called the TCR alpha chain and TCR beta chain, and these are linked by disulfide bonds. The majority of T cells (approximately 90%) in the body express TCRs with alpha and beta chains. A minority of T cells express other T-cell receptors made of different polypeptide chains, gamma and delta. Each T cell has approximately 30,000 identical antigen receptors on its cell surface. A TCR has only 1 antigen-binding site, in contrast to the B-cell receptor, which has 2, and TCRs are never secreted and always remain on the cell surface. The alpha and beta chains are encoded by different gene loci (alpha and beta TCR gene locus). The beta chain locus rearranges before the alpha chain and a functional beta chain has to be produced in order for the T cell to form a pre-T-cell receptor. The expression of the rearranged beta chain with an alpha chain precursor suppresses additional gene rearrangement at the TCR beta locus. The TCR alpha chain locus rearrangement can proceed even with production of a functional alpha chain until there is positive selection of the particular T cell. However, it is important to note that each T cell has a single functional specificity for its TCR. A key concept in understanding the immune response is that there is enormous diversity in the immune system to enable protection against a huge array of pathogens. Since the germline genome is limited in size, diversity is achieved not only by the process of V(D)J recombination but also by junctional (junctions between V-D and D-J segments) deletion of nucleotides and addition of pseudo-random, nontemplated nucleotides. In particular, the CDR3 (complementarity determining region 3), which is the most critical determinant of antigenic specificity in
T cells (and also B cells) is short (between 66-90 nucleotides, approximately 20-30 amino acids) and amenable to assessment of length by fragment length analysis, which provides a size resolution of up to 1 base pair between different CDR3 regions. It is thought that the CDR3-TCR beta chain repertoire in healthy adults contains somewhere between 3 and 4 million unique sequences.(1) Other reports suggest that the unique TCR repertoire after thymic selection is between 10 to 100 million in humans.(2) There is, however, a bias in TCR selection with overrepresentation of certain TCRs that are widely used in individuals who share the same MHC types and these are called "public TCRs." Public TCRs generally have fewer random nucleotide additions in their sequence. The TCR V beta repertoire varies significantly between individuals and populations because of 7 frequently occurring inactivating polymorphisms in functional gene segments and a large insertion/deletion-related polymorphism encompassing 2 V beta gene segments. With this latter situation, the TCR Vb 6-2/6-3 and TCR Vb 4-3 genes are frequently deleted from all ethnic groups.(3) It has been reported that the total number of functional TCR V beta gene segments expressed by an individual varies from 42 to 47.(4) Deep sequencing technologies are evolving to analyze this large diversity in the adaptive immune receptors,(5,6) however; deep sequencing of the T-cell and B-cell receptor genes is not yet widely available and is expensive. Flow cytometry-based analysis to assess TCR V beta diversity is available; however, the antibodies are limited and therefore the assay is not capable of assessing the entire TCR V beta repertoire. On the other hand, TCR beta chain repertoire analysis by fragment length analysis (spectratyping) using fluorescent primers to measure CDR3 length variability, while unable to provide the extreme high resolution of deep sequencing, can provide a global "snapshot" of T-cell receptor repertoire diversity, which is useful for most clinical applications where this level of assessment is required.(7-14) It is important to note that this method uses PCR to amplify the rearranged variable regions to provide adequate template for sequencing (fragment length analysis), and this can introduce bias due to the more efficient amplification of certain templates compared to others. However, despite this limitation, since this assay is not quantitative, it is still able to provide an assessment of diversity by measuring the CDR3 length in various TCR V beta genes, which are organized into 24 families.

**Useful For:** Assessment of T-cell receptor diversity in various clinical contexts including primary immunodeficiencies, monitoring immune reconstitution posthematopoietic cell transplantation, and temporal assessment of repertoire changes in autoimmune diseases and viral infections

**Interpretation:** An interpretive report will be provided with adult and pediatric reference values for the relative contribution of each family to the total repertoire (% diversity ratio). The interpretation will be based on visual analysis of the spectratype (polyclonal, oligoclonal, or monoclonal) for each family as well as assessment of the number of peaks (numerical value not reported), and diversity ratio (DR) (reported value). Information on the distribution of peaks, eg, Gaussian vs non-Gaussian, will also be included in the report, where appropriate. Internal analytical and quality controls will be assessed to determine the suitability of reporting a patient result. Correlation with the clinical context will be made when possible, based on clinical history provided in the patient information sheet (which should be provided with the patient sample).

**Reference Values:** References values will be provided in the patient report.

**Clinical References:**

Tea IgG

**Interpretation:** mcg/mL of IgG

**Lower Limit of Quantitation:** 2.0

**Upper Limit of Quantitation:** 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Tea, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Current as of October 11, 2018 2:20 pm CDT     800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.


**NTFPC**

**Teased Fiber (Bill Only)**

**Reference Values:**
This test is for billing purposes only.
This is not an orderable test.

**TELGP**

**Telomere Defects Gene Panel**

**Clinical Information:** Telomeres are highly specialized structures composed of TTAGGG nucleotide repeats and proteins that protect chromosome ends. Under normal circumstances, telomeres shorten with every cycle of DNA replication. Telomerase is an enzyme complex that can extend the length of the telomere, thus helping to slow the shortening process. Telomerase is most active in highly proliferative tissues such as lymphocytes, skin, intestine, and bone marrow. Variants in genes involved with telomere repair and maintenance may cause telomeres to shorten more quickly than normal. Telomere biology disorders (TBD) are a complex group of bone marrow failure syndromes (BMFS) characterized by abnormally short telomeres. The severity of these syndromes is variable, and they may present in children or adults. In addition to bone marrow failure, other symptoms of telomere biology disorders include pulmonary fibrosis, liver disease, gastrointestinal disease, and mucocutaneous abnormalities. Recognition and diagnosis of underlying TBD is important as it can help guide treatment decisions. Dyskeratosis congenita (DC) was the first TBD to be described. The subsets of DC include classic DC, Hoyeraal Hreidarsson syndrome (HHS), Revesz syndrome, DC-like conditions and isolated subtypes. Patients with the classic forms of DC are usually diagnosed in childhood, and they have a triad of mucocutaneous features including dysplastic nails, anomalies of skin pigmentation, and oral leukoplakia. Other features of DC may include bone marrow failure, gastrointestinal disease, liver disease, pulmonary fibrosis, a predisposition to certain cancers, and other medical problems. Other TBDs presenting in childhood include HHS and Revesz syndrome. TBD may also manifest in adulthood and the presentation can be variable. A broad umbrella of conditions could include bone marrow failure, pulmonary fibrosis, liver disease not otherwise classified, myelodysplastic syndrome (MDS), acute myeloid leukemia (AML) or early onset of malignancies within the DC grouping.

Telomere biology disorders can be inherited in a variety of patterns, including X-linked recessive, autosomal dominant, and autosomal recessive. At least 50% of patients with DC have mutations in the DKC1, TERC, TERT, TINF2, NHP2, and NOP10 genes. In autosomal dominant DC, phenotypes may present at a younger age and more severely in successive generations (genetic anticipation). See Table 1 for a summary of the genes included in this panel, associated diseases and the mode of inheritance. Alternatively, some patients may have 1 of these 3 features along with a hypocellular bone marrow. These patients all have very short telomeres (<1% percentile of age) in leukocytes. Patients with HHS have the features of classic DC but additionally have cerebellar hypoplasia. Telomere length analysis in leukocyte subsets is performed by flow-FISH (see references). They can also have low T cell numbers with severe B and NK cell lymphopenia (T+/-B-NK-) reminiscent of severe combined immunodeficiency (SCID). In Revesz syndrome, patients have bilateral exudative retinopathy along with other features of DC. In patients who do not meet the diagnostic criteria of DC but have several features reminiscent of the disease, a classification of DC-like may be applied. This could include presence of bone marrow failure, developmental delay, familial history of pulmonary fibrosis, and no other clear diagnosis. These patients usually have short, but not very short telomeres, and may or may
not have a genetic defect in one of the known telomere biology genes. However, these patients need careful monitoring as they may evolve into the more classic forms of DC over time. Individuals who have mutations in one of the telomere genes and have very short telomeres (<1% percentile of normal for age) who have a single feature of a telomere disorder or DC could be considered to be an isolated subtype. The stringency of monitoring depends on the individual case, age of patient, complications, and should include counseling for family members for potential disease risk and the phenomenon of genetic anticipation. Patients with aplastic anemia may have mutations in TERC, TERT, and TINF2 genes. Approximately 20% of patients with idiopathic pulmonary fibrosis (IPF) have a familial inheritance, which is autosomal dominant but with variable penetrance and approximately 30% of patients with familial IPF have short telomeres with genetic defects in the telomere genes. The genes most commonly identified in the context of IPF are TERC and TERT. The telomerase complex includes a reverse transcriptase encoded by TERT, RNA template (encoded by TERC), and associated other proteins that regulate the assembly, trafficking, recruitment of telomerase to telomeres and stability of telomeres, including dyskerin (DKC1). Other members of the telomerase complex include NOP10 (NOLA3) and NHP2 (NOLA2). The shelterin complex, which is a 6-protein complex that coats telomeres and offers telomere end protection. The shelterin complex directs telomere length homeostasis (T-loop) and prevents DNA damage response activation. The DNA helicase, RTEL1 promotes telomere elongation through the unwinding of the T-loop. TCAB1 (WRAP53) directs trafficking of the telomerase complex to the telomeric ends. The CST complex of 3 proteins (CTC1 and others) inhibits telomerase activity and promotes capping. Table 1. Genes included in the Telomere Defect PID Gene Panel GENE SYMBOL (ALIAS) PROTEIN OMIM INCIDENCE INHERITANCE PHENOTYPE DISORDER CTC1 CST complex subunit CTC1 613129 Approximately 1-3% of DC AR Cerebroretinal microangiopathy with calcifications and cysts DKC1 H/ACA ribonucleoprotein complex subunit 4 isoform 1 300126 Approximately 17-36% of DC XL Dyskeratosis congenita NHP2 H/ACA ribonucleoprotein complex subunit 2 isoform a 606470 <1% of DC AR Dyskeratosis congenita NOP10 H/ACA ribonucleoprotein complex subunit 3 606471 <1% of DC AR Dyskeratosis congenita RTEL1 Regulator of telomere elongation subunit 2 608833 Rare AR, AD Dyskeratosis congenita, pulmonary fibrosis and/or bone marrow failure, TERC Telomerase RNA component 602322 Approximately 6-10% of DC AD Dyskeratosis congenita, aplastic anemia, susceptibility to idiopathic pulmonary fibrosis TERT Telomerase reverse transcriptase isoform 1 187270 Approximately 1-7% of DC AR,AD Dyskeratosis congenita, acute myeloid leukemia, cutaneous malignant melanoma, pulmonary fibrosis and/or bone marrow failure, telomere-related TINF2 TERF1-interacting nuclear factor 2 isoform 1 604319 Approximately 11-24% of DC AD Dyskeratosis congenita, Revesz syndrome USB1 (C16ORF57) U6 snRNA phosphodiesterase isoform 1 613276 Rare AR Poikiloderma with neutropenia WRAP53 Telomerase Cajal body protein 1 (TCAB1) 612661 Approximately 3% of DC AR Dyskeratosis congenita

Useful For: Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of telomeropathies Establishing a diagnosis of a telomeropathy, in some cases, allowing for appropriate management and surveillance for disease features Identifying pathogenic variants within genes known to be associated with increased risk for telomere defects allowing for predictive testing of at-risk family members

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment. Unless reported or predicted to cause disease, alterations found deep in the intron or alterations that do not result in an amino acid substitution are not reported. Information about these variants and common polymorphisms are available upon request. The telomerase database is a useful tool for variant review and classification of telomere disorders that may be used in some cases.

Reference Values: An interpretive report will be provided.


**Temazepam (Restoril), Serum**

_**Reference Values:**_

_**Reference Range:** 50 - 1000 ng/mL_

**Terminal Deoxynucleotidyl Transferase (TdT) Immunostain, Technical Component Only**

**Clinical Information:** Terminal deoxynucleotidyl transferase (TdT) is a nuclear enzyme that adds individual nucleotides to the termini of DNA strands without the use of a DNA template. TdT is expressed normally in cortical thymocytes, immature hematopoietic stem cells, and B and T lymphoblasts. Diagnostically, TdT positivity can be helpful in confirming a diagnosis of lymphoblastic lymphoma or leukemia. Acute myeloid leukemias can also express TdT.

**Useful For:** Classification of leukemias or lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**
2. Kang LC, Dunphy CH: Immunoreactivity of MIC2 (CD99) and terminal deoxynucleotidyl transferase in bone marrow clot and core specimens of acute myeloid leukemias and myelodysplastic syndromes. Arch Pathol Lab Med 2006;130:153-157

**TERT Promoter Analysis, Tumor**

**Clinical Information:** TERT gene encodes the catalytic subunit of telomerase, an enzyme complex that regulates telomere length. TERT promoter mutations in 2 hotspots (C228T and C250T) have been shown to increase telomerase activity and contribute to tumorigenesis by allowing cancer cells to overcome cellular senescence. Among central nervous system tumors, TERT promoter mutations have primarily been identified in adults, with highest frequencies in oligodendroglioma, primary glioblastoma, solitary fibrous tumor, and medulloblastoma. Although less frequent, TERT promoter
mutations have also been observed in lower-grade infiltrating (diffuse and anaplastic) astrocytomas and ependymoma, and are rare or absent in other central nervous system tumor types. The presence of TERT promoter mutations have been associated with a less favorable prognosis in lower-grade (grade II/III) diffuse gliomas that lack IDH1/2 mutations and have intact 1p/19q (“IDH-wildtype astrocytomas”), and with a more favorable prognosis in prognosis in grade II/III IDH1/2-mutant and 1p/19q-codeleted diffuse gliomas (“IDH-mutant and 1p/19q codeleted oligodendrogliomas”). Assessment of TERT promoter mutation status in central nervous system tumors may assist in tumor classification and provide prognostically relevant information for subgroups of patients with lower-grade diffuse gliomas. TERT gene mutations are also observed in a variety of non-central nervous system (CNS) tumor types. In hepatocellular neoplasms TERT promoter mutations occur frequently in hepatocellular carcinomas and are believed to be an early step in hepatocarcinogenesis. However, TERT promoter mutations are not specific to hepatocellular carcinoma and have been reported as a key alteration in the rare progression of hepatocellular adenomas to hepatocellular carcinomas. As such, identification of a TERT promoter mutation suggests a hepatocellular neoplasm with an increased risk for aggressive behavior.

**Useful For:** Assisting in central nervous system tumor classification

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**Testosterone, Total and Bioavailable, Serum**

**Clinical Information:** Testosterone is the major androgenic hormone. It is responsible for the development of the male external genitalia and secondary sexual characteristics. In females, its main role is as an estrogen precursor. In both genders, it also exerts anabolic effects and influences behavior. In men, testosterone is secreted by the testicular Leydig cells and, to a minor extent, by the adrenal cortex. In premenopausal women, the ovaries are the main source of testosterone, with minor contributions by the adrenals and peripheral tissues. After menopause, ovarian testosterone production is significantly diminished. Testosterone production in testes and ovaries is regulated via pituitary-gonadal feedback involving luteinizing hormone (LH), and to a lesser degree, inhibins and activins. Most circulating testosterone is bound to sex hormone-binding globulin (SHBG), which in men also is called testosterone-binding globulin. A lesser fraction is albumin bound and a small proportion exists as free

**TTBS 80065**
hormone. Historically, only the free testosterone was thought to be the biologically active component. However, testosterone is weakly bound to serum albumin and dissociates freely in the capillary bed, thereby becoming readily available for tissue uptake. All non-SHBG bound testosterone is therefore considered bioavailable. During childhood, excessive production of testosterone induces premature puberty in boys and masculinization in girls. In adult women, excess testosterone production results in varying degrees of virilization, including hirsutism, acne, oligo-amenorrhea, or infertility.

Mild-to-moderate testosterone elevations are usually asymptomatic in males, but can cause distressing symptoms in females. The exact causes for mild-to-moderate elevations in testosterone often remain obscure. Common causes of pronounced elevations of testosterone include genetic conditions (eg, congenital adrenal hyperplasia), adrenal, testicular, and ovarian tumors, and abuse of testosterone or gonadotrophins by athletes. Decreased testosterone in females causes subtle symptoms. These may include some decline in libido and nonspecific mood changes. In males, it results in partial or complete degrees of hypogonadism. This is characterized by changes in male secondary sexual characteristics and reproductive function. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. In adult men, there also is a gradual modest but progressive decline in testosterone production starting between the fourth and sixth decade of life. Since this is associated with a simultaneous increase of SHBG levels, bioavailable testosterone may decline more significantly than apparent total testosterone, causing nonspecific symptoms similar to those observed in testosterone deficient females. However, severe hypogonadism consequent to aging alone is rare. Measurement of total testosterone (TTST / Testosterone, Total, Serum) is often sufficient for diagnosis, particularly if it is combined with measurements of LH (LH / Luteinizing Hormone [LH], Serum) and follicle stimulating hormone (FSH) (FSH / Follicle-Stimulating Hormone [FSH], Serum). However, these tests may be insufficient for diagnosis of mild abnormalities of testosterone homeostasis, particular if abnormalities in SHBG (SHBG / Sex Hormone Binding Globulin [SHBG], Serum) function or levels are present. Additional measurements of bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free testosterone (TGRP / Testosterone, Total and Free, Serum) are recommended in this situation. While both bioavailable and free testosterone can be used for the same indications, determination of bioavailable testosterone levels may be superior to free testosterone measurement in most situations.

**Useful For:**
- Evaluation of men with symptoms or signs of possible hypogonadism, such as loss of libido, erectile dysfunction, gynecomastia, osteoporosis, infertility
- Evaluation of boys with delayed or precocious puberty
- Monitoring testosterone replacement therapy
- Monitoring antiandrogen therapy (eg, used in prostate cancer, precocious puberty, treatment of idiopathic hirsutism, male-to-female transgender disorders)
- Evaluation of women with hirsutism, virilization, and oligo-amenorrhea
- Evaluation of women with symptoms or signs of possible testosterone deficiency
- Evaluation of infants with ambiguous genitalia or virilization
- Diagnosis of androgen-secreting tumors
- Monitoring of testosterone therapy or antiandrogen therapy in older men and in females with symptoms of testosterone deficiency
- Assessment of sex hormone-binding globulin binding abnormalities
- Assessment of functional circulating testosterone in early pubertal boys and older men
- Assessment of functional circulating testosterone in women with symptoms or signs of hyperandrogenism but normal total testosterone levels
- Monitoring of testosterone therapy or antiandrogen therapy in older men and in females

**Interpretation:**
Total Testosterone and general interpretation of testosterone abnormalities: In males:
Decreased testosterone levels indicate partial or complete hypogonadism. In hypogonadism, serum testosterone levels are usually below the reference range. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. Primary testicular failure is associated with increased luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels, and decreased total, bioavailable, and free testosterone levels. Causes include: -Genetic causes (eg, Klinefelter's syndrome, XX males) -Developmental causes (eg, testicular maldescent) -Testicular trauma or ischemia (eg, testicular torsion, surgical mishap during hernia operations) -Infections (eg, mumps) -Autoimmune diseases (eg, autoimmune polyglandular endocrine failure) -Metabolic disorders (eg, hemochromatosis, liver failure) -Ovarian dysfunction (eg, polycystic ovary syndrome) -Androgen-secreting tumors -Secondary/tertiary hypogonadism, also known as hypogonadotrophic hypogonadism, shows low testosterone and low, or inappropriately "normal," LH/FSH levels. Causes include: -Inherited or developmental disorders of hypothalamus and pituitary (eg, Kallmann's syndrome, congenital hypopituitarism) -Pituitary or hypothalamic tumors -Hyperprolactinemia of any cause -Mental retardation -Excessive exercise -Cranial irradiation -Head trauma -Medical or recreational drugs (eg,
estrogens, GNRH analogs, cannabis) Increased testosterone levels: In prepubertal boys, increased levels of testosterone are seen in precocious puberty. Further work-up is necessary to determine the cause(s) of precocious puberty. In adult men, testicular or adrenal tumors or androgen abuse might be suspected if testosterone levels exceed the upper limit of the normal range by more than 50%. Monitoring of testosterone replacement therapy: Aim of treatment is normalization of serum testosterone and LH.

During treatment with depot-testosterone preparations, trough levels of serum testosterone should still be within the normal range, while peak levels should not be significantly above the normal young adult range. Monitoring of antiandrogen therapy: Aim is usually to suppress testosterone levels to castrate levels or below (no more than 25% of the lower reference range value). In females: Decreased testosterone levels may be observed in primary or secondary ovarian failure, analogous to the situation in men, alongside the more prominent changes in female hormone levels. Most women with oophorectomy have a significant decrease in testosterone levels. Increased testosterone levels may be seen in: -Congenital adrenal hyperplasia. Nonclassical (mild) variants may not present in childhood, but during or after puberty. In addition to testosterone, multiple other androgens or androgen precursors, such as 17 OH-progesterone (OHPG / 17-Hydroxyprogesterone, Serum), are elevated, often to a greater degree than testosterone. -Analogue to males, but at lower levels in prepubertal girls, increased levels of testosterone are seen in precocious puberty. -Ovarian or adrenal neoplasms. High estrogen values also may be observed and LH and FSH are low or "normal." Testosterone-producing ovarian or adrenal neoplasms often produce total testosterone values above 200 ng/dL. -Polycystic ovarian syndrome. Hirsutism, acne, menstrual disturbances, insulin resistance and, frequently, obesity form part of this syndrome. Total testosterone levels may be normal or mildly elevated and uncommonly exceed 200 ng/dL. Monitoring of testosterone replacement therapy: The efficacy of testosterone replacement in females is under study. If it is used, then levels should be kept within the normal female range at all times. Bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free testosterone (TGRP / Testosterone, Total and Free, Serum) levels should also be monitored to avoid overtreatment.

Monitoring of antiandrogen therapy: Antiandrogen therapy is most commonly employed in the management of mild-to-moderate idiopathic female hyperandrogenism, as seen in polycystic ovarian syndrome. Total testosterone levels are a relatively crude guideline for therapy and can be misleading. Therefore, bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free testosterone (TGRP / Testosterone, Total and Free, Serum) also should be monitored to ensure treatment adequacy. However, there are no universally agreed biochemical end points and the primary treatment end point is the clinical response. Testosterone, Total and Bioavailable: Usually, bioavailable (and free testosterone) levels parallel the total testosterone levels. However, a number of conditions and medications are known to increase or decrease the sex hormone-binding globulin (SHBG) concentration, which may cause total testosterone concentration to change without necessarily influencing the bioavailable or free testosterone concentration, or vice versa: -Treatment with corticosteroids and sex steroids (particularly oral conjugated estrogen) can result in changes in SHBG levels and availability of sex-steroid binding sites on SHBG. This may make diagnosis of subtle testosterone abnormalities difficult. -Inherited abnormalities in SHBG binding. -LIVER disease and severe systemic illness. -In pubertal boys and adult men, mild decreases of total testosterone without LH abnormalities can be associated with delayed puberty or mild hypogonadism. In this case, either bioavailable or free testosterone measurements are known to increase or decrease the SHBG concentration, which may cause total testosterone concentration to change without necessarily influencing the bioavailable or free testosterone concentration, or vice versa: -Treatment with corticosteroids and sex steroids (particularly oral conjugated estrogen) can result in changes in SHBG levels and availability of sex-steroid binding sites on SHBG. This may make diagnosis of subtle testosterone abnormalities difficult. -Inherited abnormalities in SHBG binding. -LIVER disease and severe systemic illness. -In pubertal boys and adult men, mild decreases of total testosterone without LH abnormalities can be associated with delayed puberty or mild hypogonadism. In this case, either bioavailable or free testosterone measurements are better indicators of mild hypogonadism than determination of total testosterone levels. -In polycystic ovarian syndrome and related conditions, there is often significant insulin resistance, which is associated with low SHBG levels. -Consequently, bioavailable or free testosterone levels may be more significantly elevated. Either bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free testosterone (TGRP / Testosterone, Total and Free, Serum) should be used as supplemental tests to total testosterone in the above situations. The correlation coefficient between bioavailable and free testosterone (by equilibrium dialysis) is 0.9606. However, bioavailable testosterone is usually the preferred test, as it more closely reflects total bioactive testosterone, particularly in older men. These men not only have elevated SHBG levels, but albumin levels may also vary, due to coexisting illnesses.

Reference Values:
TESTOSTERONE, TOTAL
Males
0-5 months: 75-400 ng/dL
6 months-9 years: <7-20 ng/dL
10-11 years: <7-130 ng/dL
12-13 years: <7-800 ng/dL
<table>
<thead>
<tr>
<th>Age Range</th>
<th>Total Testosterone (ng/dL)</th>
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<tr>
<td>14 years</td>
<td>&lt;7-1,200</td>
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<tr>
<td>15-16 years</td>
<td>100-1,200</td>
</tr>
<tr>
<td>17-18 years</td>
<td>300-1,200</td>
</tr>
<tr>
<td>&gt; or =19 years</td>
<td>240-950</td>
</tr>
</tbody>
</table>

**Tanner Stages**

- I (prepubertal): <7-20
- II: 8-66
- III: 26-800
- IV: 85-1,200
- V (young adult): 300-950

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**TESTOSTERONE, BIOAVAILABLE**

**Males**

- < or =19 years: not established
- 20-29 years: 83-257 ng/dL
- 30-39 years: 72-235 ng/dL
- 40-49 years: 61-213 ng/dL
- 50-59 years: 50-190 ng/dL
- 60-69 years: 40-168 ng/dL
- > or =70 years: not established

**Females (non-oophorectomized)**

- < or =19 years: not established
- 20-50 years (on oral estrogen): 0.8-4.0 ng/dL
- 20-50 years (not on oral estrogen): 0.8-10 ng/dL
- >50 years: not established

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**Clinical References:**
role is as an estrogen precursor. In both genders, it also exerts anabolic effects and influences behavior. In men, testosterone is secreted by the testicular Leydig cells and, to a minor extent, by the adrenal cortex. In premenopausal women, the ovaries are the main source of testosterone with minor contributions by the adrenals and peripheral tissues. After menopause, ovarian testosterone production is significantly diminished. Testosterone production in testes and ovaries is regulated via pituitary-gonadal feedback involving luteinizing hormone (LH) and, to a lesser degree, inhibins and activins. Most circulating testosterone is bound to sex hormone-binding globulin (SHBG), which in men also is called testosterone-binding globulin. A lesser fraction is albumin bound and a small proportion exists as free hormone. Historically, only the free testosterone was thought to be the biologically active component. However, testosterone is weakly bound to serum albumin and dissociates freely in the capillary bed, thereby becoming readily available for tissue uptake. All non-SHBG-bound testosterone is therefore considered bioavailable. During childhood, excessive production of testosterone induces premature puberty in boys and masculinization in girls. In adult women, excess testosterone production results in varying degrees of virilization, including hirsutism, acne, oligo-amenorrhea, or infertility. Mild-to-moderate testosterone elevations are usually asymptomatic in males, but can cause distressing symptoms in females. The exact causes for mild-to-moderate elevations in testosterone often remain obscure. Common causes of pronounced elevations of testosterone include genetic conditions (eg, congenital adrenal hyperplasia); adrenal, testicular, and ovarian tumors; and abuse of testosterone or gonadotrophins by athletes. Decreased testosterone in females causes subtle symptoms. These may include some decline in libido and nonspecific mood changes. In males, it results in partial or complete degrees of hypogonadism. This is characterized by changes in male secondary sexual characteristics and reproductive function. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. In adult men, there also is a gradual modest, but progressive, decline in testosterone production starting between the fourth and sixth decades of life. Since this is associated with a simultaneous increase of SHBG levels, bioavailable testosterone may decline more significantly than apparent total testosterone, causing nonspecific symptoms similar to those observed in testosterone deficient females. However, severe hypogonadism, consequent to aging alone, is rare. Measurement of total testosterone (TTST / Testosterone, Total, Serum) is often sufficient for diagnosis, particularly if it is combined with measurements of LH and follicle-stimulating hormone (FSH) (LH / Luteinizing Hormone [LH], Serum and FSH / Follicle-Stimulating Hormone [FSH], Serum). However, these tests may be insufficient for diagnosis of mild abnormalities of testosterone homeostasis, particularly if abnormalities in SHBG (SHBG / Sex Hormone Binding Globulin [SHBG], Serum) function or levels are present. Additional measurements of free testosterone or bioavailable testosterone are recommended in this situation; bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) is the preferred assay.

**Useful For:** Alternative, second-level test for suspected increases or decreases in physiologically active testosterone (preferred: TTBS / Testosterone, Total and Bioavailable, Serum); indications: -Assessment of androgen status in cases with suspected or known sex hormone-binding globulin-binding abnormalities -Assessment of functional circulating testosterone in early pubertal boys and older men -Assessment of functional circulating testosterone in women with symptoms or signs of hyperandrogenism, but normal total testosterone levels -Monitoring of testosterone therapy or antiandrogen therapy in older men and in females

**Interpretation:** Total testosterone and general interpretation of testosterone abnormalities: Males: Decreased testosterone levels indicate partial or complete hypogonadism. Serum testosterone levels are usually below the reference range. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. Primary testicular failure is associated with increased luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, and decreased total, bioavailable, and free testosterone levels. Causes include: -Genetic causes (eg, Klinefelter syndrome, XXX males) -Developmental causes (eg, testicular maldescent) -Testicular trauma or ischemia (eg, testicular torsion, surgical mishap during hernia operations) -Infections (eg, mumps) -Autoimmune diseases (eg, autoimmune polyglandular endocrine failure) -Metabolic disorders (eg, hemochromatosis, liver failure) -Orchidectomy Secondary/tertiary hypogonadism, also known as hypogonadotrophic hypogonadism, shows low testosterone and low, or inappropriately "normal," LH/FSH levels; causes include: -Inherited or developmental disorders of hypothalamus and pituitary (eg, Kallmann syndrome, congenital hypopituitarism) -Pituitary or hypothalamic tumors -Hyperprolactinemia of any cause -Malnutrition or excessive exercise -Cranial irradiation -Head trauma -Medical or recreational drugs (eg,
estrogens, GNRH analogs, cannabis) Increased testosterone levels: -In prepubertal boys, increased levels of testosterone are seen in precocious puberty. Further workup is necessary to determine the causes of precocious puberty. -In adult men, testicular or adrenal tumors or androgen abuse might be suspected if testosterone levels exceed the upper limit of the normal range by more than 50%. Monitoring of testosterone replacement therapy: Aim of treatment is normalization of serum testosterone and LH. During treatment with depot-testosterone preparations, trough levels of serum testosterone should still be within the normal range, while peak levels should not be significantly above the normal young adult range. Monitoring of antiandrogen therapy: Aim is usually to suppress testosterone levels to castrate levels or below (no more than 25% of the lower reference range value). Females: Decreased testosterone levels may be observed in primary or secondary ovarian failure, analogous to the situation in men, alongside the more prominent changes in female hormone levels. Most women with oophorectomy have a significant decrease in testosterone levels. Increased testosterone levels may be seen in: -Congenital adrenal hyperplasia: nonclassical (mild) variants may not present in childhood but during or after puberty. In addition to testosterone, multiple other androgens or androgen precursors are elevated, such as 17OH-progesterone (OHPG / 17-Hydroxyprogesterone, Serum), often to a greater degree than testosterone. -Prepubertal girls: analogous to males, but at lower levels, increased levels of testosterone are seen in precocious puberty. -Ovarian or adrenal neoplasms: high estrogen values also may be observed, and LH and FSH are low or "normal." Testosterone-producing ovarian or adrenal neoplasms often produce total testosterone values above 200 ng/dL. -Polycystic ovarian syndrome: hirsutism, acne, menstrual disturbances, insulin resistance and, frequently, obesity, form part of this syndrome. Total testosterone levels may be normal or mildly elevated and uncommonly above 200 ng/dL. Monitoring of testosterone replacement therapy: The efficacy of testosterone replacement in females is under study. If it is used, total testosterone levels should be kept within the normal female range at all times. Bioavailable or free testosterone levels also should be monitored to avoid over treatment. Monitoring of antiandrogen therapy: Antiandrogen therapy is most commonly employed in the management of mild-to-moderate "idiopathic" female hyperandrogenism, as seen in polycystic ovarian syndrome. Total testosterone levels are a relatively crude guideline for therapy and can be misleading. Therefore, bioavailable or free testosterone also should be monitored to ensure treatment adequacy. However, there are no universally agreed biochemical end points and the primary treatment end point is the clinical response. Free testosterone: Usually, bioavailable and free testosterone levels parallel the total testosterone levels. However, a number of conditions and medications are known to increase or decrease the sex hormone-binding globulin (SHBG) (SHBG / Sex Hormone Binding Globulin [SHBG], Serum) concentration, which may cause total testosterone concentration to change without necessarily influencing the bioavailable or free testosterone concentration, or vice versa: -Treatment with corticosteroids and sex steroids (particularly oral conjugated estrogen) can result in changes in SHBG levels and availability of sex-steroid binding sites on SHBG. This may make diagnosis of subtle testosterone abnormalities difficult. -Inherited abnormalities in SHBG binding -Liver disease and severe systemic illness -In pubertal boys and adult men, mild decreases of total testosterone without LH abnormalities can be associated with delayed puberty or mild hypogonadism. In this case, either bioavailable or free testosterone measurements are better indicators of mild hypogonadism than determination of total testosterone levels. -In polycystic ovarian syndrome and related conditions, there is often significant insulin resistance, which is associated with low SHBG levels. Consequently, bioavailable or free testosterone levels may be more significantly elevated. Either bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free testosterone (TGRP / Testosterone Total and Free, Serum) should be used as supplemental tests to total testosterone in the above situations. The correlation coefficient between bioavailable and free testosterone (by equilibrium dialysis) is 0.9606. However, bioavailable testosterone is usually the preferred test, as it more closely reflects total bioactive testosterone, particularly in older men. Older men not only have elevated SHBG levels, but albumin levels also may vary due to coexisting illnesses.

Reference Values:

TESTOSTERONE, FREE

Males (adult):
- 20-<25 years: 5.25-20.7 ng/dL
- 25-<30 years: 5.05-19.8 ng/dL
- 30-<35 years: 4.85-19.0 ng/dL
- 35-<40 years: 4.65-18.1 ng/dL
- 40-<45 years: 4.46-17.1 ng/dL
- 45-<50 years: 4.26-16.4 ng/dL
50-<55 years: 4.06-15.6 ng/dL
55-<60 years: 3.87-14.7 ng/dL
60-<65 years: 3.67-13.9 ng/dL
65-<70 years: 3.47-13.0 ng/dL
70-<75 years: 3.28-12.2 ng/dL
75-<80 years: 3.08-11.3 ng/dL
80-<85 years: 2.88-10.5 ng/dL
85-<90 years: 2.69-9.61 ng/dL
90-<95 years: 2.49-8.76 ng/dL
95-100+ years: 2.29-7.91 ng/dL

Males (children):
<1 year: Term infants

1-15 days: 0.20-3.10 ng/dL*
16 days-1 year: Values decrease gradually from newborn (0.20-3.10 ng/dL) to prepubertal levels
*Citation: J Clin Endocrinol Metab 1973;36(6):1132-1142

1-8 years: <0.04-0.11 ng/dL
9 years: <0.04-0.45 ng/dL
10 years: <0.04-1.26 ng/dL
11 years: <0.04-5.52 ng/dL
12 years: <0.04-9.28 ng/dL
13 years: <0.04-12.6 ng/dL
14 years: 0.48-15.3 ng/dL
15 years: 1.62-17.7 ng/dL
16 years: 2.93-19.5 ng/dL
17 years: 4.28-20.9 ng/dL
18 years: 5.40-21.8 ng/dL
19 years: 5.36-21.2 ng/dL

Females (adult):
20-<25 years: 0.06-1.08 ng/dL
25-<30 years: 0.06-1.06 ng/dL
30-<35 years: 0.06-1.03 ng/dL
35-<40 years: 0.06-1.00 ng/dL
40-<45 years: 0.06-0.98 ng/dL
45-<50 years: 0.06-0.95 ng/dL
50-<55 years: 0.06-0.92 ng/dL
55-<60 years: 0.06-0.90 ng/dL
60-<65 years: 0.06-0.87 ng/dL
65-<70 years: 0.06-0.84 ng/dL
70-<75 years: 0.06-0.82 ng/dL
75-<80 years: 0.06-0.79 ng/dL
80-<85 years: 0.06-0.76 ng/dL
85-<90 years: 0.06-0.73 ng/dL
90-<95 years: 0.06-0.71 ng/dL
95-100+ years: 0.06-0.68 ng/dL

Females (children):
<1 year: Term infants

1-15 days: 0.06-0.25 ng/dL*
16 days-1 year: Values decrease gradually from newborn (0.06-0.25 ng/dL) to prepubertal levels
*Citation: J Clin Endocrinol Metab, 36(6):1132-1142, 1973

1-4 years: <0.04 ng/dL
5 years: <0.04-0.07 ng/dL
6 years: <0.04-0.14 ng/dL
7 years: <0.04-0.23 ng/dL
8 years: <0.04-0.34 ng/dL
9 years: <0.04-0.46 ng/dL
10 years: <0.04-0.59 ng/dL
11 years: <0.04-0.72 ng/dL
12 years: <0.04-0.84 ng/dL
13 years: <0.04-0.96 ng/dL
14 years: <0.04-1.06 ng/dL
15-18 years: <0.04-1.09 ng/dL
19 years: 0.06-1.08 ng/dL

TESTOSTERONE, TOTAL
Males
0-5 months: 75-400 ng/dL
6 months-9 years: <7-20 ng/dL
10-11 years: <7-130 ng/dL
12-13 years: <7-800 ng/dL
14 years: <7-1,200 ng/dL
15-16 years: 100-1,200 ng/dL
17-18 years: 300-1,200 ng/dL
> or =19 years: 240-950 ng/dL

Tanner Stages*
I (prepubertal): <7-20
II: 8-66
III: 26-800
IV: 85-1,200
V (young adult): 300-950

Females
0-5 months: 20-80 ng/dL
6 months-9 years: <7-20 ng/dL
10-11 years: <7-44 ng/dL
12-16 years: <7-75 ng/dL
17-18 years: 20-75 ng/dL
> or =19 years: 8-60 ng/dL

Tanner Stages*
I (prepubertal): <7-20
II: <7-47
III: 17-75
IV: 20-75
V (young adult): 12-60

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

Testosterone, Total, Bioavailable, and Free, Serum

Clinical Information: Testosterone is the major androgenic hormone. It is responsible for the development of the male external genitalia and secondary sexual characteristics. In females, its main role is as an estrogen precursor. In both genders, it also exerts anabolic effects and influences behavior. In men, testosterone is secreted by the testicular Leydig cells and, to a minor extent, by the adrenal cortex. In premenopausal women, the ovaries are the main source of testosterone with minor contributions by the adrenals and peripheral tissues. After menopause, ovarian testosterone production is significantly diminished. Testosterone production in testes and ovaries is regulated via pituitary-gonadal feedback involving luteinizing hormone (LH) and, to a lesser degree, inhibins and activins. Most circulating testosterone is bound to sex hormone-binding globulin (SHBG), which in men also is called testosterone-binding globulin. A lesser fraction is albumin bound and a small proportion exists as free hormone. Historically, only the free testosterone was thought to be the biologically active component. However, testosterone is weakly bound to serum albumin and dissociates freely in the capillary bed, thereby becoming readily available for tissue uptake. All non-SHBG-bound testosterone is therefore considered bioavailable. During childhood, excessive production of testosterone induces premature puberty in boys and masculinization in girls. In adult women, excess testosterone production results in varying degrees of virilization, including hirsutism, acne, oligo-amenorrhea, or infertility.

Mild-to-moderate testosterone elevations are usually asymptomatic in males, but can cause distressing symptoms in females. The exact causes for mild-to-moderate elevations in testosterone often remain obscure. Common causes of pronounced elevations of testosterone include genetic conditions (eg, congenital adrenal hyperplasia); adrenal, testicular, and ovarian tumors; and abuse of testosterone or gonadotrophins by athletes. Decreased testosterone in females causes subtle symptoms. These may include some decline in libido and nonspecific mood changes. In males, it results in partial or complete degrees of hypogonadism. This is characterized by changes in male secondary sexual characteristics and reproductive function. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. In adult men, there also is a gradual modest, but progressive, decline in testosterone production starting between the fourth and sixth decades of life. Since this is associated with a simultaneous increase of SHBG levels, bioavailable testosterone may decline more significantly than apparent total testosterone, causing nonspecific symptoms similar to those observed in testosterone deficient females. However, severe hypogonadism, consequent to aging alone, is rare. Measurement of total testosterone (TTST / Testosterone, Total, Serum) is often sufficient for diagnosis, particularly if it is combined with measurements of LH and follicle-stimulation hormone (FSH) (LH / Luteinizing Hormone [LH], Serum and FSH / Follicle-Stimulating Hormone [FSH], Serum). However, these tests may be insufficient for diagnosis of mild abnormalities of testosterone homeostasis, particularly if abnormalities in SHBG (SHBG / Sex Hormone Binding Globulin [SHBG], Serum) function or levels are present. Additional measurements of free testosterone or bioavailable testosterone are recommended in this situation; bioavailable testosterone (see TTBS / Testosterone, Total and Bioavailable, Serum) is the preferred assay.

Useful For: Second- or third-order test for evaluating testosterone status (eg, when abnormalities of sex hormone-binding globulin are present)

Interpretation: Total Testosterone and General Interpretation of Testosterone Abnormalities: Males: Decreased testosterone levels indicate partial or complete hypogonadism. Serum testosterone levels are usually below the reference range. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. Primary testicular failure is associated with increased luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels, and decreased total, bioavailable, and free testosterone levels. Causes include: -Genetic causes (eg, Klinefelter syndrome, XX males) -Developmental causes (eg, testicular maldescent) -Testicular trauma or ischemia (eg, testicular torsion, surgical mishap during hernia operations) -Infections (eg, mumps) -Autoimmune diseases (eg, autoimmune polyglandular endocrine failure) -Metabolic disorders (eg, hemochromatosis, liver failure) -Orchidectomy Secondary/tertiary hypogonadism, also known as hypogonadotrophic hypogonadism, shows low testosterone and low, or inappropriately "normal," LH/FSH levels; causes include: -Inherited or developmental disorders of hypothalamus and pituitary (eg, Kallmann syndrome, congenital hypopituitarism) -Pituitary or hypothalamic tumors -Hyperprolactinemia of any cause -Malnutrition or excessive exercise -Cranial irradiation -Head trauma -Medical or recreational drugs (eg, estrogens, GNRH analogs, cannabis) Increased testosterone levels: -In prepubertal boys, increased levels of testosterone are seen in precocious puberty. Further workup is necessary to determine the causes of precocious puberty. -In adult men, testicular or adrenal tumors or androgen abuse might be suspected if testosterone levels exceed
the upper limit of the normal range by more than 50%. Monitoring of testosterone replacement therapy: Aim of treatment is normalization of serum testosterone and LH. During treatment with depot-testosterone preparations, trough levels of serum testosterone should still be within the normal range, while peak levels should not be significantly above the normal young adult range. Monitoring of antiandrogen therapy: Aim is usually to suppress testosterone levels to castrate levels or below (no more than 25% of the lower reference range value). Females: Decreased testosterone levels may be observed in primary or secondary ovarian failure, analogous to the situation in men, alongside the more prominent changes in female hormone levels. Most women with oophorectomy have a significant decrease in testosterone levels. Increased testosterone levels may be seen in: -Congenital adrenal hyperplasia: nonclassical (mild) variants may not present in childhood but during or after puberty. In addition to testosterone, multiple other androgens or androgen precursors are elevated, such as 17OHP (17-Hydroxyprogesterone, Serum), often to a greater degree than testosterone. -Prepubertal girls: analogous to males, but at lower levels, increased levels of testosterone are seen in precocious puberty. -Ovarian or adrenal neoplasms: high estrogen values also may be observed, and LH and FSH are low or "normal." Testosterone-producing ovarian or adrenal neoplasms often produce total testosterone values greater than 200 ng/dL. -Polycystic ovarian syndrome: hirsutism, acne, menstrual disturbances, insulin resistance and, frequently, obesity, form part of this syndrome. Total testosterone levels may be normal or mildly elevated and, uncommonly, greater than 200 ng/dL. Monitoring of testosterone replacement therapy: The efficacy of testosterone replacement in females is under study. If it is used, total testosterone levels should be kept within the normal female range at all times. Bioavailable or free testosterone levels also should be monitored to avoid overtreatment. Monitoring of antiandrogen therapy: Antiandrogen therapy is most commonly employed in the management of mild-to-moderate "idiopathic" female hyperandrogenism, as seen in polycystic ovarian syndrome. Total testosterone levels are a relatively crude guideline for therapy and can be misleading. Therefore, bioavailable or free testosterone also should be monitored to ensure treatment adequacy. However, there are no universally agreed biochemical endpoints and the primary treatment end point is the clinical response. Bioavailable and Free Testosterone: Usually, bioavailable and free testosterone levels parallel the total testosterone levels. However, a number of conditions and medications are known to increase or decrease the SHBG (SHBG / Sex Hormone Binding Globulin [SHBG], Serum) concentration, which may cause total testosterone concentration to change without necessarily influencing the bioavailable or free testosterone concentration, or vice versa: -Treatment with corticosteroids and sex steroids (particularly oral conjugated estrogen) can result in changes in SHBG levels and availability of sex-steroid binding sites on SHBG. This may make diagnosis of subtle testosterone abnormalities difficult. -Inherited abnormalities in SHBG binding. -Liver disease and severe systemic illness. -In pubertal boys and adult men, mild decreases of total testosterone without LH abnormalities can be associated with delayed puberty or mild hypogonadism. In this case, either bioavailable or free testosterone measurements are better indicators of mild hypogonadism than determination of total testosterone levels. -In polycystic ovarian syndrome and related conditions, there is often significant insulin resistance, which is associated with low SHBG levels. Consequently, bioavailable or free testosterone levels may be more significantly elevated. Either bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free (TGRP / Testosterone Total and Free, Serum) testosterone should be used as supplemental tests to total testosterone in the above situations. The correlation coefficient between bioavailable and free testosterone (by equilibrium dialysis) is 0.9606. However, bioavailable testosterone is usually the preferred test, as it more closely reflects total bioactive testosterone, particularly in older men. Older men not only have elevated SHBG levels, but albumin levels also may vary due to coexisting illnesses.

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17-18 years: 300-1,200 ng/dL
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Tanner Stages*

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  Page 2173
I (prepubertal): <7-20
II: 8-66
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0-5 months: 20-80 ng/dL
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12-16 years: <7-75 ng/dL
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Tanner Stages*
I (prepubertal): <7-20
II: <7-47
III: 17-75
IV: 20-75
V (young adult): 12-60

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.

TESTOSTERONE, FREE
Males (adult):
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40-<45 years: 4.46-17.1 ng/dL
45-<50 years: 4.26-16.4 ng/dL
50-<55 years: 4.06-15.6 ng/dL
55-<60 years: 3.87-14.7 ng/dL
60-<65 years: 3.67-13.9 ng/dL
65-<70 years: 3.47-13.0 ng/dL
70-<75 years: 3.28-12.2 ng/dL
75-<80 years: 3.08-11.3 ng/dL
80-<85 years: 2.88-10.5 ng/dL
85-<90 years: 2.69-9.61 ng/dL
90-<95 years: 2.49-8.76 ng/dL
95-100+ years: 2.29-7.91 ng/dL

Males (children):
<1 year: Term infants
1-15 days: 0.20-3.10 ng/dL*
16 days-1 year: Values decrease gradually from newborn (0.20-3.10 ng/dL) to prepubertal levels
*Citation: J Clin Endocrinol Metab 1973;36(6):1132-1142

1-8 years: <0.04-0.11 ng/dL
9 years: <0.04-0.45 ng/dL
10 years: <0.04-1.26 ng/dL
11 years: <0.04-5.52 ng/dL
12 years: <0.04-9.28 ng/dL
13 years: <0.04-12.6 ng/dL
14 years: 0.48-15.3 ng/dL
15 years: 1.62-17.7 ng/dL
16 years: 2.93-19.5 ng/dL
17 years: 4.28-20.9 ng/dL
18 years: 5.40-21.8 ng/dL
19 years: 5.36-21.2 ng/dL

Females (adult):

20-<25 years: 0.06-1.08 ng/dL
25-<30 years: 0.06-1.06 ng/dL
30-<35 years: 0.06-1.03 ng/dL
35-<40 years: 0.06-1.00 ng/dL
40-<45 years: 0.06-0.98 ng/dL
45-<50 years: 0.06-0.95 ng/dL
50-<55 years: 0.06-0.92 ng/dL
55-<60 years: 0.06-0.90 ng/dL
60-<65 years: 0.06-0.87 ng/dL
65-<70 years: 0.06-0.84 ng/dL
70-<75 years: 0.06-0.82 ng/dL
75-<80 years: 0.06-0.79 ng/dL
80-<85 years: 0.06-0.76 ng/dL
85-<90 years: 0.06-0.73 ng/dL
90-<95 years: 0.06-0.71 ng/dL
95-100+ years: 0.06-0.68 ng/dL

Females (children):

<1 year: Term infants

1-15 days: 0.06-0.25 ng/dL*
16 days-1 year: Values decrease gradually from newborn (0.06-0.25 ng/dL) to prepubertal levels
*Citation: J Clin Endocrinol Metab 1973;36(6):1132-1142

1-4 years: <0.04 ng/dL
5 years: <0.04-0.07 ng/dL
6 years: <0.04-0.14 ng/dL
7 years: <0.04-0.23 ng/dL
8 years: <0.04-0.34 ng/dL
9 years: <0.04-0.46 ng/dL
10 years: <0.04-0.59 ng/dL
11 years: <0.04-0.72 ng/dL
12 years: <0.04-0.84 ng/dL
13 years: <0.04-0.96 ng/dL
14 years: <0.04-1.06 ng/dL
15-18 years: <0.04-1.09 ng/dL
19 years: 0.06-1.08 ng/dL

TESTOSTERONE, BIOAVAILABLE

Males

< or =19 years: not established
20-29 years: 83-257 ng/dL
30-39 years: 72-235 ng/dL
40-49 years: 61-213 ng/dL
50-59 years: 50-190 ng/dL
60-69 years: 40-168 ng/dL
70-75 years: not established
76-80 years: not established
81-85 years: not established
86-90 years: not established
90-95 years: not established
96-100 years: not established

Females (non-oophorectomized)

< or =19 years: not established
20-50 years (on oral estrogen): 0.8-4.0 ng/dL
20-50 years (not on oral estrogen): 0.8-10 ng/dL
>50 Years: not established


Testosterone, Total, Serum

Clinical Information: Testosterone is the major androgenic hormone. It is responsible for the development of the male external genitalia and secondary sexual characteristics. In females, its main role is as an estrogen precursor. In both genders, it also exerts anabolic effects and influences behavior. In males, testosterone is secreted by the testicular Leydig cells and, to a minor extent, by the adrenal cortex. In premenopausal women, the ovaries are the main source of testosterone with minor contributions by the adrenals and peripheral tissues. After menopause, ovarian testosterone production is significantly diminished. Testosterone production in testes and ovaries is regulated via pituitary-gonadal feedback involving luteinizing hormone (LH) and, to a lesser degree, inhibins and activins. Most circulating testosterone is bound to sex hormone-binding globulin (SHBG), which in males is also called testosterone-binding globulin. A lesser fraction is albumin bound and a small proportion exists as free hormone. Historically, only the free testosterone was thought to be the biologically active component. However, testosterone is weakly bound to serum albumin and dissociates freely in the capillary bed, thereby becoming readily available for tissue uptake. All non-SHBG-bound testosterone is therefore considered bioavailable. During childhood, excessive production of testosterone induces premature puberty in boys and masculinization in girls. In adult women, excess testosterone production results in varying degrees of virilization, including hirsutism, acne, oligomenorrhea, or infertility. Mild-to-moderate testosterone elevations are usually asymptomatic in males, but can cause distressing symptoms in females. The exact cause for mild-to-moderate elevations of testosterone often remains obscure. Common causes of pronounced elevations include genetic conditions (e.g., congenital adrenal hyperplasia), adrenal, testicular, and ovarian tumors, and abuse of testosterone or gonadotrophins by athletes. Decreased testosterone in females causes subtle symptoms. These may include some decline in libido and nonspecific mood changes. In males, it results in partial or complete degrees of hypogonadism. This is characterized by changes in male secondary sexual characteristics and reproductive function. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. In adult males, there also is a gradual modest, but progressive, decline in testosterone production starting between the fourth and sixth decade of life. Since this is associated with a simultaneous increase of SHBG levels, bioavailable testosterone may decline more significantly than apparent total testosterone, causing nonspecific symptoms similar to those observed in testosterone deficient females. However, severe hypogonadism, consequent to aging alone, is rare. Measurement of total testosterone is often sufficient for diagnosis, particularly if it is combined with measurements of LH (LH / Luteinizing Hormone [LH], Serum) and follicle stimulating hormone (FSH) (FSH / Follicle-Stimulating Hormone [FSH], Serum). However, these tests may be insufficient for diagnosis of mild abnormalities of testosterone homeostasis, particularly if abnormalities in SHBG (SHBG / Sex Hormone Binding Globulin [SHBG], Serum) function or levels are present. Additional measurements of bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free testosterone (TGRP / Testosterone Total and Free, Serum) are recommended in this situation. See Steroid Pathways in Special Instructions.

Useful For: Evaluation of men with symptoms or signs of possible hypogonadism, such as loss of libido, erectile dysfunction, gynecomastia, osteoporosis, or infertility Evaluation of boys with delayed or precocious puberty Monitoring testosterone replacement therapy Monitoring antiandrogen therapy (e.g. used in prostate cancer, precocious puberty, treatment of idiopathic hirsutism, male-to-female transgender disorders, etc.) Evaluation of women with hirsutism, virilization, and oligomenorrhea Evaluation of women with symptoms or signs of possible testosterone deficiency Evaluation of infants with ambiguous genitalia or virilization Diagnosis of androgen-secreting tumors
Interpretation: In males: Decreased testosterone levels indicate partial or complete hypogonadism. In hypogonadism, serum testosterone levels are usually below the reference range. The cause is either primary or secondary/tertiary (pituitary/hypothalamic) testicular failure. Primary testicular failure is associated with increased luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, and decreased total, bioavailable, and free testosterone levels. Causes include: -Genetic causes (eg, Klinefelter syndrome, XX males) -Developmental causes (eg, testicular maldescent) -Testicular trauma or ischemia (eg, testicular torsion, surgical mishap during hernia operations) -Infections (eg, mumps) -Autoimmune diseases (eg, autoimmune polyglandular endocrine failure) -Metabolic disorders (eg, hemochromatosis, liver failure) -Orchidectomy Secondary/tertiary hypogonadism, also known as hypogonadotropic hypogonadism, shows low testosterone and low, or inappropriately “normal” LH/FSH levels. Causes include: -Inherited or developmental disorders of hypothalamus and pituitary (eg, Kallmann syndrome, congenital hypopituitarism) -Pituitary or hypothalamic tumors -Hyperprolactinemia of any cause -Malnutrition -Excessive exercise -Cranial irradiation -Head trauma -Medical or recreational drugs (eg, estrogens, gonadotropin releasing hormone [GNRH] analogs, cannabis) Increased testosterone levels: -In prepubertal boys, increased levels of testosterone are seen in precocious puberty. Further workup is necessary to determine the cause(s) of precocious puberty. -In adult males, testicular or adrenal tumors or androgen abuse might be suspected if testosterone levels exceed the upper limit of the normal range by more than 50%. Monitoring of testosterone replacement therapy: Aim of treatment is normalization of serum testosterone and LH. During treatment with depot-testosterone preparations, trough levels of serum testosterone should still be within the normal range, while peak levels should not be significantly above the normal young adult range. Monitoring of antiandrogen therapy: Aim is usually to suppress testosterone levels to castrate levels or below (no more than 25% of the lower reference range value, typically <50% ng/dL). In females: Decreased testosterone levels may be observed in primary or secondary ovarian failure, analogous to the situation in men, alongside the more prominent changes in female hormone levels. Most women with oophorectomy have a significant decrease in testosterone levels. Increased testosterone levels may be seen in: -Congenital adrenal hyperplasia. Nonclassical (mild) variants may not present in childhood, but during or after puberty. In addition to testosterone, multiple other androgens or androgen precursors, such as 17 OH-progesterone (OHPG / 17-Hydroxyprogesterone, Serum), are elevated, often to a greater degree than testosterone. -Analogous to males, but at lower levels in prepubertal girls, increased levels of testosterone are seen in precocious puberty. -Ovarian or adrenal neoplasms. High estrogen values also may be observed and LH and FSH are low or “normal.” Testosterone-producing ovarian or adrenal neoplasms often produce total testosterone values above 200 ng/dL. -Polycystic ovarian syndrome. Hirsutism, acne, menstrual disturbances, insulin resistance and, frequently, obesity form part of this syndrome. Total testosterone levels may be normal or mildly elevated and uncommonly above 200 ng/dL. Monitoring of testosterone replacement therapy: The efficacy of testosterone replacement in females is under study. If it is used, then levels should be kept within the normal female range at all times. Bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free testosterone (TGRP / Testosterone, Total and Free, Serum) levels should also be monitored to avoid overtreatment. Monitoring of antiandrogen therapy: Antiandrogen therapy is most commonly employed in the management of mild-to-moderate idiopathic female hyperandrogenism, as seen in polycystic ovarian syndrome. Total testosterone levels are a relatively crude guideline for therapy and can be misleading. Therefore, bioavailable (TTBS / Testosterone, Total and Bioavailable, Serum) or free testosterone (TGRP / Testosterone, Total and Free, Serum) also should be monitored to ensure treatment adequacy. However, there are no universally agreed biochemical end points and the primary treatment end point is the clinical response. See Steroid Pathways in Special Instructions.

Reference Values:
Males
0-5 months: 75-400 ng/dL
6 months-9 years: <7-20 ng/dL
10-11 years: <7-130 ng/dL
12-13 years: <7-800 ng/dL
14 years: <7-1,200 ng/dL
15-16 years: 100-1,200 ng/dL
17-18 years: 300-1,200 ng/dL
> or =19 years: 240-950 ng/dL
Tanner Stages*
I (prepubertal): <7-20
II: 8-66
III: 26-800
IV: 85-1,200
V (young adult): 300-950

Females
0-5 months: 20-80 ng/dL
6 months-9 years: <7-20 ng/dL
10-11 years: <7-44 ng/dL
12-16 years: <7-75 ng/dL
17-18 years: 20-75 ng/dL
> or =19 years: 8-60 ng/dL

Tanner Stages*
I (prepubertal): <7-20
II: <7-47
III: 17-75
IV: 20-75
V (young adult): 12-60

*Puberty onset (transition from Tanner stage I to Tanner stage II) occurs for boys at a median age of 11.5 (+/-2) years and for girls at a median age of 10.5 (+/-2) years. There is evidence that it may occur up to 1 year earlier in obese girls and in African American girls. For boys, there is no definite proven relationship between puberty onset and body weight or ethnic origin. Progression through Tanner stages is variable. Tanner stage V (young adult) should be reached by age 18.


TTIGS

Tetanus Toxoid IgG Antibody, Serum

Clinical Information: Tetanus results from contamination of wounds or lacerations with Clostridium tetani spores from the environment. The spores germinate to actively replicating bacterial cells localized within the wound and produce the heat-labile toxin, tetanospasmin. Tetanospasmin attaches to peripheral nerve endings and travels to the central nervous system (CNS) where it blocks inhibitory impulses to motor neurons and leads to severe, spastic muscle contractions, a classic characteristic of tetanus. The disease is preventable by vaccination with tetanus toxoid (formaldehyde-treated tetanospasmin), which stimulates development of antitetanus toxoid antibodies. In the United States, tetanus toxoid is administered to children as part of the combined diphtheria, tetanus, and acellular pertussis (TdaP) vaccine. Two to 3 weeks following vaccination, a patient's immunological response may be assessed by measuring the total antitetanus toxoid IgG antibody level in serum. An absence of antibody formation postvaccination may relate to immune deficiency disorders, either congenital or acquired, or iatrogenic due to immunosuppressive drugs.

Useful For: Assessment of an antibody response to the tetanus toxoid vaccine, which should be performed at least 3 weeks after immunization. An aid to diagnose immunodeficiency

Interpretation: Results > or =0.01 suggest a vaccine response. A tetanus toxoid booster should strongly be considered for patients with anti-tetanus toxoid IgG values between 0.01 and 0.5 IU/mL.
Some cases of tetanus, usually mild, have occasionally been observed in patients who have a measurable serum level of 0.01 to 1.0 IU/mL.

**Reference Values:**
- Vaccinated: Positive (> or = 0.01 IU/mL)
- Unvaccinated: Negative (< 0.01 IU/mL)

**Clinical References:**

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**TETOX 82138**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effecter cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>1</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>2</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>4</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

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### Tetrahydrobiopterin and Neopterin Profile (BH4, N)

**Clinical Information:** CSF Neopterin/Tetrahydrobiopterin (NC03) is useful for diagnosis of certain disorders of neurotransmitter metabolism. This testing may also be used for assessment of Variants of Uncertain Significance (VUS) identified during genetic testing (e.g. Next Generation Sequencing or Capillary Sequencing Testing). CLINICAL Tetrahydrobiopterin (BH4) serves as a cofactor for the hydroxylation of phenylalanine and in the biosynthesis of biogenic amines. Deficiency of BH4 may occur as a result of mutations causing a reduction in one of the three biosynthetic enzymes, guanosine triphosphate cyclohydrolase, 6-pyruvoyl-tetrahydropterin synthase, sepiapterin reductase, or the two regenerating enzymes, pterin-4-carbinolamine dehydratase, and dihydropteridine reductase. Defects in BH4 metabolism can result in hyperphenylalaninemia and deficiency of the neurotransmitters dopamine and serotonin. Changes in CSF neopterin may also occur in deficiency of the BH4 synthesis pathway. Disorders of BH4 metabolism are characterized by a wide range of symptoms that may include developmental delay, mental disability, behavioral disturbances, dystonia, Parkinsonian symptoms, gait disturbances, speech delay, psychomotor retardation and ptosis.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>BH4 (nmol/L)</th>
<th>Neop (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 0.2</td>
<td>40 – 105</td>
<td>7 – 65</td>
</tr>
<tr>
<td>0.2 – 0.5</td>
<td>23 – 98</td>
<td>7 – 65</td>
</tr>
<tr>
<td>0.5 – 2.0</td>
<td>18 – 58</td>
<td>7 – 65</td>
</tr>
<tr>
<td>2.0 – 5.0</td>
<td>18 – 50</td>
<td>7 – 65</td>
</tr>
<tr>
<td>5.0 – 10</td>
<td>9 – 40</td>
<td>7 – 40</td>
</tr>
<tr>
<td>10 – 15</td>
<td>9 – 32</td>
<td>8 – 33</td>
</tr>
<tr>
<td>Adults</td>
<td>10 – 30</td>
<td>8 - 28</td>
</tr>
</tbody>
</table>

Note: If test results are consistent with the clinical presentation, please call our laboratory to discuss the case and/or submit a second sample for confirmatory testing. An important consideration for false positive for false negative results is the improper labeling of the patient sample.

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### Thalassemia and Hemoglobinopathy Evaluation

**Clinical Information:** This consultative study has the ability to test for the detection of almost all known hemoglobin disorders in an economical manner. Because this can include multiple tests for alpha-thalassemias, beta-thalassemias, delta-beta-thalassemia, hereditary persistence of fetal hemoglobin (HPFH) and for all known Hb variants, an expert in these disorders can guide testing to explain the clinical question or CBC values. This evaluation is particularly useful for complete classification of compound combinations of Hb S with alpha- or beta-thalassemia, Hb E/beta-0-thalassemia, and many other complex thalassemic disorders. Since iron deficiency can mimic thalassemias, ferritin levels are measured to evaluate this possibility. Hemoglobin disorders include those associated with thalassemias (decreased protein quantity) and hemoglobin variants (abnormal protein production). Many are clinically harmless and others cause symptoms including microcytosis, sickling disorders, hemolysis,
erythrocytosis, cyanosis/hypoxia, long-standing or familial anemia, compensated or episodic anemia, and increased methemoglobin or sulfhemoglobin results. Hemoglobin disorders can show autosomal recessive or autosomal dominant inheritance patterns. The thalassemias are a group of disorders of hemoglobin (Hb) synthesis. Normal adult Hb consists of 2 alpha globin chains (encoded by 2 pairs of alpha globin genes, each pair located on chromosome 16), and 2 beta globin chains (encoded by 2 beta globin genes, each located on chromosome 11). Thalassemia syndromes result from an underproduction of 1 or 2 types of globin chains and are characterized by the type (alpha, beta, delta) and magnitude of underproduction (number of defective genes) and the severity of clinical symptoms (minor, intermedia, major). The severity of the clinical and hematologic effects is directly related to the imbalance of alpha-like to beta-like chains. The most common form of thalassemia is alpha thalassemia. Hemoglobin H (Hb H) disease, results from dysfunction of 3 alpha chains, and shows a variable phenotype with most showing moderate anemia. The deletion of all 4 alpha chains is incompatible with life. Affected fetuses are hydropic and die in utero or shortly after premature birth. The blood smears show large hypochromic red cells, nucleated red cells, target cells, and red cell fragments. Hb Barts, Hb H, and Hb Portland are present in significant quantities. It is the most common cause of hydrops fetalis in Southeast Asia and southern China.

**Useful For:** Extensive and economical diagnosis and classification of hemoglobinopathies or thalassemia including complex disorders Evaluation of microcytosis Diagnosis of hereditary persistence of hemoglobin (HPFH)

**Interpretation:** A hematopathologist expert in these disorders evaluates the case, appropriate tests are performed, and an interpretive report is issued.

**Reference Values:**
Definitive results and an interpretive report will be provided.


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**Thallium, 24 Hour, Urine**

**Clinical Information:** Thallium is found in some depilatories and rodenticides. Accidental ingestion may lead to vomiting, diarrhea, and leg pains followed by a severe and sometimes fatal sensorimotor polyneuropathy and renal failure. Alopecia (hair loss) may occur 3 weeks after poisoning. The fatal dose is approximately 1 g.

**Useful For:** Detecting toxic thallium exposure in 24-hour urine specimens

**Interpretation:** Normal daily output is less than 1 mcg/day. Exposed patients can have urine output greater than 10 mcg/day. The long-term consequences of such an exposure are poor.

**Reference Values:**
0-17 years: not established
≥ or =18 years: <2 mcg/24 hour

**Clinical References:**

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**Thallium, Blood**

**Clinical Information:** Thallium is a by-product of lead smelting. The clinical interest in thallium derives primarily from its use as a rodenticide since this is the most frequent route of human exposure. Thallium is rapidly absorbed via ingestion, inhalation, skin contact, and through the mucous membranes.
of the mouth, gastrointestinal tract, and lungs. It is considered to be as toxic as lead and mercury, with similar sites of action. The mechanism of action of thallium is: -Competition with potassium at cell receptors to affect ion pumps -Inhibition of DNA synthesis -Binds to sulfhydryl groups on proteins in neural axons -Concentrates in renal tubular cells and reacts with protein to cause necrosis Patients exposed to high doses of thallium (>1 g) present with alopecia (hair loss), peripheral neuropathy and seizures, and renal failure.

**Useful For:** Detecting toxic thallium exposure in whole blood specimens

**Interpretation:** Normal blood concentrations are less than 1 ng/mL. Significant exposure is associated with thallium concentrations in blood greater than 10 ng/mL, and as high as 50 ng/mL. The long-term sequelae from such an exposure is poor.

**Reference Values:**

- 0-17 years: not established
- > or =18 years: <2 ng/mL

**Clinical References:**


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**TLCRU**

**60325**

**Thallium/Creatinine Ratio, Random, Urine**

**Clinical Information:** Thallium is found in some depilatories and rodenticides. Accidental ingestion may lead to vomiting, diarrhea, and leg pains followed by a severe and sometimes fatal sensorimotor polyneuropathy. Alopecia (hair loss) may occur 3 weeks after poisoning. The fatal dose is approximately 1 gram.

**Useful For:** Detecting toxic thallium exposure in random urine specimens

**Interpretation:** Patients exposed to high doses of thallium (>1 g) present with alopecia, peripheral neuropathy and seizures, and renal failure. Normal daily output is less than 1 mcg/day. Exposed patients can have urine output greater than 10 mcg/day. The long-term consequences of such an exposure are poor.

**Reference Values:**

- 0-17 years: not established
- > or =18 years: <2 mcg/g creatinine

**Clinical References:**


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**FFTCC**

**75149**

**THC Confirmation, MS, SP**

**Interpretation:** Assay threshold: 1.0 ng/mL

**Reference Values:**

- Negative

Units: ng/mL

Test Performed by: Medtox Laboratories, Inc.
402 W. County Road D
St. Paul, MN 55112

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**THEOA**

**Theophylline, Serum**

Current as of October 11, 2018 2:20 pm CDT
800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com

Page 2182
**Clinical Information:** Theophylline and its congener, aminophylline, are used to relax smooth muscles of the bronchial airways and pulmonary blood vessels to relieve and prevent symptoms of asthma and bronchospasm. Theophylline is administered orally at a dose of 400 mg/day or 6 mg/kg, whichever is lower, or intravenously as aminophylline at 0.6 mg/kg/hour. Oral dosage may be increased at 200-mg increments to a maximum of 900 mg/day, or 13 mg/kg if the steady-state blood concentration is within the therapeutic range of 8.0 to 20.0 mcg/mL. Theophylline has a half-life of 4 hours in children and adult smokers, and 7 hours in nonsmoking adults, thus steady-state is reached in approximately 1 day. The volume of distribution is 0.5 L/kg, and the drug is approximately 50% protein bound. Theophylline exhibits zero-order clearance kinetics like phenytoin, small increases in dose yield disproportionately large increases in blood concentration. Coadministration of cimetidine and erythromycin will significantly inhibit theophylline clearance, requiring dosage reduction. Other drugs such as allopurinol, ciprofloxacin, oral contraceptives, and propranolol inhibit theophylline clearance to a lesser degree. Smoking induces the synthesis of cytochrome P448, the antipyrine-dependent cytochrome, which significantly increases the rate of metabolism of theophylline. Drugs such as phenobarbital, phenytoin, carbamazepine, and rifampin slightly increase the rate at which the drug is cleared. Theophylline exhibits rather severe toxicity that is proportional to blood level.

**Useful For:** Assessing and adjusting dosage for optimal therapeutic level Assessing toxicity

**Interpretation:** Response to theophylline is directly proportional to serum level. Patients usually receive the best response when the serum level is above 8.0 mcg/mL, with minimal toxicity experienced as long as the level is less than or equal to 20.0 mcg/mL.

**Reference Values:**
**Therapeutic:**
- Bronchodilation: 8.0-20.0 mcg/mL
- Neonatal apnea (< or =4 weeks old): 6.0-13.0 mcg/mL
- Critical value: >20.0 mcg/mL

**Clinical References:**

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**Thermoactinomyces vulgaris, IgG Antibodies, Serum**

**Clinical Information:** Thermoactinomyces vulgaris is one of the causative agents of hypersensitivity pneumonitis (HP). Other causative microorganisms include Micropolyspora faeni and Aspergillus fumigatus. The development of HP caused by Thermoactinomyces vulgaris is accompanied by an immune response to Thermoactinomyces vulgaris antigens with production of IgG antibodies. While the immunopathogenesis of HP is not known, several immune mechanisms are postulated to play a role, including both cellular and humoral mechanisms.(1)

**Useful For:** Evaluation of patients suspected of having hypersensitivity pneumonitis induced by exposure to Thermoactinomyces vulgaris

**Interpretation:** Elevated concentrations of IgG antibodies to Thermoactinomyces vulgaris, Aspergillus fumigatus, or Micropolyspora faeni in patients with signs and symptoms of hypersensitivity pneumonitis may be consistent with disease caused by exposure to 1 or more of these organic antigens.

**Reference Values:**
- 0-12 years: < or =6.6 mg/L
- 13-18 years: < or =11.0 mg/L
- >18 years: < or =23.9 mg/L

**Clinical References:**
1. Fink JN, Zacharisen MC: Chapter 69: Hypersensitivity pneumonitis. In
Thiamine (Vitamin B1), Whole Blood

Clinical Information: Thiamine (vitamin B1) is an essential vitamin required for carbohydrate metabolism, brain function, and peripheral nerve myelination. Thiamine is obtained from the diet. Body stores are limited and deficiencies can develop quickly. The total thiamine pool in the average adult is about 30 mg. An intake of 0.5 mg per 1,000 kcal per day is needed to maintain this pool. Due to its relatively short storage time, marginal deficiency can occur within 10 days and more severe deficiency within 21 days if intake is restricted. Approximately 80% of all chronic alcoholics are thiamine deficient due to poor nutrition. However, deficiency also can occur in individuals who are elderly, have chronic gastrointestinal problems, have marked anorexia, are on cancer treatment, or are receiving diuretic therapy. The signs and symptoms of mild-to-moderate thiamine deficiency are nonspecific and may include poor sleep, malaise, weight loss, irritability, and confusion. Newborns breast fed from deficient mothers may develop dyspnea and cyanosis; diarrhea, vomiting, and aphonia may follow. Moderate deficiency can affect intellectual performance and well-being, despite a lack of apparent clinical symptoms. Severe deficiency causes congestive heart failure (wet beriberi), peripheral neuropathy (dry beriberi), Wernicke encephalopathy (a medical emergency that can progress to coma and death), and Korsakoff syndrome (an often irreversible memory loss and dementia that can follow). Rapid treatment of Wernicke encephalopathy with thiamine can prevent Korsakoff syndrome. Symptoms of dry beriberi include poor appetite, fatigue, and peripheral neuritis. Symptoms of wet beriberi include cardiac failure and edema. Patients with Wernicke encephalopathy present with behavior change (confusion, delirium, apathy), diplopia (often sixth nerve palsies), and ataxia. A late stage, in which the patients may develop an irreversible amnestic confabulatory state, is referred to as the Wernicke-Korsakoff syndrome. The response to thiamine therapy in deficient patients is usually rapid. Thiamine deficiency is a treatable, yet underdiagnosed, disorder in the United States. A heightened level of awareness of the possibility of thiamine deficiency is necessary to identify, intervene, and prevent thiamine deficiency’s dire consequences. It appears that no conditions are directly attributable to thiamine excess and that thiamine administration is safe except in extremely rare cases of anaphylaxis from intravenous thiamin. Whole blood thiamine testing is superior to currently available alternative tests for assessing thiamine status. Serum or plasma thiamine testing suffers from poor sensitivity and specificity, and <10% of blood thiamine is contained in plasma. Transketolase determination, once considered the most reliable means of assessing thiamine status, is now considered an inadequate method. The transketolase method is an indirect assessment. Since transketolase activity requires thiamin, decreased transketolase activity is presumed to be due to the decrease of thiamin. However, the test is somewhat nonspecific, as other factors may decrease transketolase activity. Transketolase is less sensitive than liquid chromatography-tandem mass spectrometry (LC-MS/MS), has poor precision, and specimen stability concerns. Thiamine diphosphate is the active form of thiamine and is most appropriately measured to assess thiamine status. Thiamine diphosphate in circulating blood is present in erythrocytes, but is undetectable (present in very low levels) in plasma or serum. LC-MS/MS analysis of thiamine diphosphate in whole blood or erythrocytes is the most sensitive, specific, and precise method for determining the nutritional status of thiamine and is a reliable indicator of total body stores. This assay specifically targets and quantitates the active form of vitamin B1 (thiamine diphosphate) as an indicator of vitamin B1 status.

Useful For: Assessment of thiamine deficiency Thiamine measurement in patients with behavioral changes, eye signs, gait disturbances, delirium, and encephalopathy; or in patients with questionable nutritional status, especially those who appear at risk and who also are being given insulin for hyperglycemia

Interpretation: Values for thiamine diphosphate of less than 70 nmol/L are suggestive of thiamine deficiency.

Reference Values: 70-180 nmol/L

ThinPrep Diagnostic

Clinical Information: The ThinPrep Pap test is an alternative preparation method for the cervical Pap screening test. The method utilizes a liquid-based technique that replaces the direct smear method of the conventional Pap screen. This method is one of several technologies developed to improve visualization of cellular material by reducing smearing trauma, air drying artifact, and obscuring blood and inflammation. In addition, variability in smearing technique is eliminated as the majority of processing and preparation is performed in the laboratory under controlled conditions. Squamous cell carcinoma of the cervix is believed to develop in progressive stages from normal through precancerous (dysplastic) stages, to carcinoma in situ, and eventually invasive carcinoma. This sequence is felt to develop over a matter of years in most patients. Follow-up of the cervical Pap abnormality atypical squamous cells of undetermined significance (ASCUS) is costly and frustrating to patients and clinicians because a large percentage of these patients have normal colposcopic and biopsy findings. Yet, a significant percentage (10%-15%) will have an underlying high-grade squamous intraepithelial lesion (HSIL).

Useful For: Diagnostic test for detection of cervical carcinoma or intraepithelial lesions when screening women for possible cervical neoplasia

Interpretation: Standard reporting, as defined by the Bethesda System (TBS) is utilized.

Reference Values:
Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.

Note: Abnormal results will be reviewed by a pathologist at an additional charge.


ThinPrep Diagnostic with Human Papillomavirus (HPV) Reflex

Clinical Information: Squamous cell carcinoma of the cervix is believed to develop in progressive stages from normal through precancerous (dysplastic) stages, to carcinoma in situ, and eventually invasive carcinoma. This sequence is felt to develop over a matter of years in most patients. Follow-up of the cervical Pap abnormality atypical squamous cells of undetermined significance (ASCUS) is costly and frustrating to patients and clinicians because a large percentage of these patients have normal colposcopic and biopsy findings. Yet, a significant percentage (10%-15%) will have an underlying high-grade squamous intraepithelial lesion (HSIL). The majority (>99%) of cervical epithelial neoplasms are the result of human papillomavirus (HPV) infection. High-risk HPV (HR-HPV) types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) can result in both low-grade squamous intraepithelial lesions and HSIL, as well as invasive carcinomas. Patients with HSIL have a greater risk
for progression to carcinoma. In the setting of an abnormal Pap result, the presence of HR-HPV types in cervical specimens identifies a subgroup of patients with a greater likelihood of having a HSIL. If the patient has been previously diagnosed with an abnormal Pap result or is at high risk, considering ordering this test, which is diagnostic, rather than the screen (STHPV / ThinPrep Screen with Human Papillomavirus [HPV] Reflex). Persistent infection with HPV is the principal cause of cervical cancer and its precursor cervical intraepithelial neoplasia (CIN).(1-3) The presence of HPV has been implicated in more than 99% of cervical cancers worldwide. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8,000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPV that can infect the human anogenital mucosa. However, data suggest that 14 of these types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high-risk for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic, and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers.(4-6) Although persistent infection with HR-HPV is necessary for the development of cervical cancer and its precursor lesions, only a very small percentage of infections progress to these disease states. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. An infection with any HPV type can produce CIN although this also usually resolves once the HPV infection has been cleared. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to detect early precursors to cervical cancer. Although it has decreased the death rates due to cervical cancer dramatically in those countries, the Pap smear and subsequent liquid-based cytology methods require subjective interpretation by highly trained cytopathologists and misinterpretation can occur. Cytological abnormalities are primarily due to infection with HPV; however, various inflammatory conditions or sampling variations can result in false-positive cytology results. Triage of an abnormal cytology result may involve repeat testing, colposcopy and biopsy. A histologically confirmed high-grade lesion must be surgically removed or ablated in order to prevent the development of invasive cervical cancer. Nucleic acid (DNA) testing by PCR has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may 1) increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology and 2) reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance (ASC-US). Recently, data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 or HPV-18 positive women is 11.4% (95% confidence interval [CI] 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for other HR-HPV genotypes and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV negative women.(7) Based in part on these data, the American Society for Colposcopy and Cervical Pathology (ASCCP) now recommends that HPV 16 and 18 genotyping be performed on women who are positive for HR-HPV but negative by routine cytology. Women who are found to be positive for HPV-16 or HPV-18 may be referred to colposcopy, while women who are negative for genotypes 16 and 18 may have repeat cytology and HR-HPV testing in 12 months.(4)

### Useful For:
Management and triage of patients age 21 years or older with abnormal Papanicolaou (Pap) results Diagnostic test for detection of human papillomavirus (HPV) high-risk genotypes associated with the development of cervical cancer Results can be used as an aid in triaging women with abnormal Pap smear results Individual genotyping of HPV-16 or HPV-18, if present Results of HPV-16 and HPV-18 genotyping can be used as an aid in triaging women with positive high-risk HPV (HR-HPV) but negative Pap smear results

### Interpretation:
Cytology: Standard reporting, as defined by the Bethesda System (TBS) is utilized. Human papillomavirus (HPV): A positive result indicates the presence of HPV DNA due to 1 or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous cells of undetermined significance (ASC-US) Papanicolaou (Pap) smear result and who are positive for high-risk HPV (HR-HPV), consider referral for colposcopy, if clinically indicated. For women aged 30 years and
older with a negative Pap smear result, but who are positive for HPV-16 or HPV-18, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear, positive HR-HPV test result, but who are negative for HPV-16 and HPV-18, consider repeat testing by both cytology and a HR-HPV test in 12 months.

Reference Values:

ThinPrep PANANICOLAOU
Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.
Note: Abnormal results will be reviewed by a pathologist at an additional charge.

HUMAN PAPILLOMAVIRUS (HPV)
Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

Clinical References:

TPRPS
70332

ThinPrep Screen

Clinical Information: The ThinPrep Pap test is an alternative preparation method for the cervical Pap screening test. The method utilizes a liquid-based technique that replaces the direct smear method of the conventional Pap screen. This method is one of several technologies developed to improve visualization of cellular material by reducing smearing trauma, air drying artifact, and obscuring blood and inflammation. In addition, variability in smearing technique is eliminated as the majority of processing and preparation is performed in the laboratory under controlled conditions. Squamous cell carcinoma of the cervix is believed to develop in progressive stages from normal through precancerous (dysplastic) stages, to carcinoma in situ, and eventually invasive carcinoma. This sequence is felt to develop over a matter of years in most patients. Follow-up of the cervical Pap abnormality atypical squamous cells of undetermined significance (ASCUS) is costly and frustrating to patients and clinicians because a large percentage of these patients have normal colposcopic and biopsy findings. Yet, a significant percentage (10%-15%) will have an underlying high-grade squamous intraepithelial lesion (HSIL).

Useful For: Screening test for detection of cervical carcinoma or intraepithelial lesions when screening women for possible cervical neoplasia

Interpretation: Standard reporting, as defined by the Bethesda System (TBS) is utilized.

Reference Values:
Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.
Note: Abnormal results will be reviewed by a pathologist at an additional charge.

STHPV 70335

ThinPrep Screen with Human Papillomavirus (HPV) Reflex

Clinical Information: Squamous cell carcinoma of the cervix is believed to develop in progressive stages from normal through precancerous (dysplastic) stages, to carcinoma in situ, and eventually invasive carcinoma. This sequence is felt to develop over a matter of years in most patients. Follow-up of the cervical Pap abnormality atypical squamous cells of undetermined significance (ASCUS) is costly and frustrating to patients and clinicians because a large percentage of these patients have normal colposcopic and biopsy findings. Yet, a significant percentage (10%-15%) will have an underlying high-grade squamous intraepithelial lesion (HSIL). The majority (>99%) of cervical epithelial neoplasms are the result of human papillomavirus (HPV) infection. High-risk HPV (HR-HPV) types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) can result in both low-grade squamous intraepithelial lesions and HSIL as well as invasive carcinomas. Patients with HSIL have a greater risk for progression to carcinoma. In the setting of an abnormal Pap result, the presence of HR-HPV types in cervical specimens identifies a subgroup of patients with a greater likelihood of having a HSIL. If the patient has been previously diagnosed with an abnormal Pap result or is at high risk, considering ordering the diagnostic test: DTHPV / ThinPrep Diagnostic with Human Papillomavirus (HPV) Reflex rather than this screen. Persistent infection with HPV is the principal cause of cervical cancer and its precursor cervical intraepithelial neoplasia (CIN). (1-3) The presence of HPV has been implicated in >99% of cervical cancers worldwide. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8,000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPV types that can infect the human anogenital mucosa. However, data suggest that 14 of these types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high-risk for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic, and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers. (4-6) Although persistent infection with HR-HPV is necessary for the development of cervical cancer and its precursor lesions, only a very small percentage of infections progress to these disease states. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. An infection with any HPV type can produce CIN although this also usually resolves once the HPV infection has been cleared. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to detect early precursors to cervical cancer. Although it has decreased the death rates due to cervical cancer dramatically in those countries, the Pap smear and subsequent liquid-based cytology methods require subjective interpretation by highly trained cytopathologists and misinterpretation can occur. Cytological abnormalities are primarily due to infection with HPV; however, various inflammatory conditions or sampling variations can result in false-positive cytology results. Triage of an abnormal cytology result may involve repeat testing, colposcopy and biopsy. A histologically confirmed high-grade lesion must be surgically removed or ablated in order to prevent the development of invasive cervical cancer. Nucleic acid (DNA) testing by PCR has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may 1) increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology and 2) reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance.
(ASC-US). Recently, data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 or HPV-18 positive women is 11.4% (95% confidence interval [CI] 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for other HR-HPV genotypes and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV negative women.(7) Based in part on these data, the American Society for Colposcopy and Cervical Pathology (ASCP) now recommends that HPV 16/18 genotyping be performed on women who are positive for HR-HPV but negative by routine cytology. Women who are found to be positive for HPV-16 or -18 may be referred to colposcopy, while women who are negative for genotypes 16 and 18 may have repeat cytology and HR-HPV testing in 12 months.(4)

**Useful For:** Management and triage of patients, age 21 or greater, with abnormal Pap results

Screening test for detection of human papillomavirus (HPV) high-risk genotypes associated with the development of cervical cancer Aids in triaging women with abnormal Pap smear results Individual genotyping of HPV-16 and HPV-18, if present Aids in triaging women with positive HR-HPV but negative Pap smear results

**Interpretation:** Cytology: Standard reporting, as defined by the Bethesda System (TBS) is utilized. Human papillomavirus (HPV): A positive result indicates the presence of HPV DNA due to 1 or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous cells of undetermined significance (ASC-US) Pap smear result and who are positive for high-risk HPV (HR-HPV), consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear result but who are positive for HPV-16 or HPV-18, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear, positive HR-HPV test result, but who are negative for HPV-16 and HPV-18, consider repeat testing by both cytology and a HR-HPV test in 12 months.

**Reference Values:**

- ThinPrep PAPANICOLAOU
  Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.

- HUMAN PAPILLOMAVIRUS (HPV)
  Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

**Clinical References:**

Co-Test-Diagnostic

Clinical Information: The majority (>99%) of cervical epithelial neoplasms are the result of human papillomavirus (HPV) infection. High-risk HPV (HR-HPV) types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) can result in both low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL), as well as invasive carcinoma. (1,2) Patients with both negative cytology and negative HPV have been shown to be at extremely low risk for cervical neoplasia. (1,2) For women 30 years and older who have received a negative Pap test and concurrent negative HPV result, the American Cancer Society (ACS) and American College of Obstetricians and Gynecologists (ACOG) recommendations for cervical screening state that physicians may lengthen the screening interval to 3 years when using the combined tests. Patients deemed to be at high risk by the clinician should still be screened more frequently. The presence of HR-HPV types in cervical specimens identifies a subgroup of patients with a greater likelihood of having a high-grade squamous intraepithelial lesion. Current guidelines for follow-up of a cytology-negative/HPV-positive patient recommend repeat HPV testing in 12 months. (2) Persistent infection with HPV is the principal cause of cervical cancer and its precursor cervical intraepithelial neoplasia (CIN). (1-3) The presence of HPV has been implicated in more than 99% of cervical cancers worldwide. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8,000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPV's that can infect the human anogenital mucosa. However, data suggest that 14 of these types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high risk for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic, and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers. (4-6) Although persistent infection with HR-HPV is necessary for the development of cervical cancer and its precursor lesions, only a very small percentage of infections progress to these disease states. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. An infection with any HPV type can produce CIN although this also usually resolves once the HPV infection has been cleared. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to detect early precursors to cervical cancer. Although it has decreased the death rates due to cervical cancer dramatically in those countries, the Pap smear and subsequent liquid-based cytology methods require subjective interpretation by highly trained cytopathologists and misinterpretation can occur. Cytological abnormalities are primarily due to infection with HPV; however, various inflammatory conditions or sampling variations can result in false-positive cytology results. Triage of an abnormal cytology result may involve repeat testing, colposcopy and biopsy. A histologically confirmed high-grade lesion must be surgically removed or ablated in order to prevent the development of invasive cervical cancer. Nucleic acid (DNA) testing by PCR has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may 1) increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology and 2) reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance (ASC-US). Recently, data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 and HPV-18 positive women is 11.4% (95% confidence interval [CI] 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for other HR-HPV genotypes and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV negative women. (7) Based in part on these data, the American Society for Colposcopy and Cervical Pathology (ASCCP) now recommends that HPV 16 and 18 genotyping be performed on women who are positive for HR-HPV but negative by routine cytology. Women who are found to be positive for HPV-16 or HPV-18 may be referred to colposcopy, while women who are negative for genotypes 16 and 18 may have repeat cytology and HR-HPV testing in 12 months. (4)

Useful For: Diagnostic test for detection of cervical carcinoma or intraepithelial lesions and the presence or absence of high-risk human papillomavirus (HR-HPV) in women over age 30 at risk for cervical neoplasia HPV testing detection of high risk genotypes associated with the development of cervical cancer Results can be used as an aid in triaging women with abnormal Pap smear results.
Individual genotyping of HPV-16 or HPV-18, if present. Results of HPV-16 and HPV-18 genotyping can be used as an aid in triaging women with positive HR-HPV but negative Pap smear results.

**Interpretation:** Cytology: Standard reporting, as defined by the Bethesda System (TBS) is utilized. Human papillomavirus (HPV): A positive result indicates the presence of HPV DNA due to 1 or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous cells of undetermined significance (ASC-US) Pap smear result and who are positive for high-risk HPV (HR-HPV), consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear result, but who are positive for HPV-16 or HPV-18, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear, positive HR-HPV test result, but who are negative for HPV-16 and HPV-18, consider repeat testing by both cytology and a HR-HPV test in 12 months.

**Reference Values:**

**HUMAN PAPILLOMAVIRUS (HPV)**

Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

**Clinical References:**

1. Lorincz AT, Richart RM: Human papillomavirus DNA testing as an adjunct to cytology in cervical screening programs. Arch Pathol Lab Med 2003 August;127(8):959-968
been implicated in more than 99% of cervical cancers worldwide. HPV is a small, nonenveloped, double-stranded DNA virus, with a genome of approximately 8,000 nucleotides. There are more than 118 different types of HPV and approximately 40 different HPV genotypes that can infect the human anogenital mucosa. However, data suggest that 14 of these types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) are considered high risk for the development of cervical cancer and its precursor lesions. Furthermore, HPV types 16 and 18 have been regarded as the genotypes most closely associated with progression to cervical cancer. HPV-16 is the most carcinogenic and is associated with approximately 60% of all cervical cancers, while HPV-18 accounts for approximately 10% to 15% of cervical cancers. Although persistent infection with HR-HPV is necessary for the development of cervical cancer and its precursor lesions, only a very small percentage of infections progress to these disease states. Sexually transmitted infection with HPV is extremely common, with estimates of up to 75% of all women being exposed to HPV at some point. However, almost all infected women will mount an effective immune response and clear the infection within 2 years without any long-term health consequences. An infection with any HPV type can produce CIN although this also usually resolves once the HPV infection has been cleared. In developed countries with cervical cancer screening programs, the Pap smear has been used since the mid-1950s as the primary tool to detect early precursors to cervical cancer. Although it has decreased the death rates due to cervical cancer dramatically in those countries, the Pap smear and subsequent liquid-based cytology methods require subjective interpretation by highly trained cytopathologists and misinterpretation can occur. Cytological abnormalities are primarily due to infection with HPV; however, various inflammatory conditions or sampling variations can result in false-positive cytology results. Triage of an abnormal cytology result may involve repeat testing, colposcopy, and biopsy. A histologically confirmed high-grade lesion must be surgically removed or ablated in order to prevent the development of invasive cervical cancer. Nucleic acid (DNA) testing by PCR has become a standard, noninvasive method for determining the presence of a cervical HPV infection. Proper implementation of nucleic acid testing for HPV may 1) increase the sensitivity of cervical cancer screening programs by detecting high-risk lesions earlier in women 30 years and older with normal cytology and 2) reduce the need for unnecessary colposcopy and treatment in patients 21 and older with cytology results showing atypical squamous cells of undetermined significance (ASC-US). Recently, data suggest that individual genotyping for HPV types 16 and 18 can assist in determining appropriate follow-up testing and triaging women at risk for progression to cervical cancer. Studies have shown that the absolute risk of CIN-2 or worse in HPV-16 and HPV-18 positive women is 11.4% (95% confidence interval [CI] 8.4%-14.8%) compared with 6.1% (95% CI, 4.9%-7.2%) of women positive for other HR-HPV genotypes and 0.8% (95% CI, 0.3%-1.5%) in HR-HPV negative women. Based in part on these data, the American Society for Colposcopy and Cervical Pathology (ASCCP) now recommends that HPV 16/18 genotyping be performed on women who are positive for HR-HPV but negative by routine cytology. Women who are found to be positive for HPV-16 or HPV-18 may be referred to colposcopy, while women who are negative for genotypes 16 and 18 may have repeat cytology and HR-HPV testing in 12 months.

Useful For: Screening for cervical carcinoma or intraepithelial lesions and the presence or absence of high-risk human papillomavirus (HR-HPV) when screening women over the age of 30 for possible cervical neoplasia. Human papillomavirus (HPV) testing detection of high-risk genotypes associated with the development of cervical cancer. Aids in triaging women with abnormal Pap smear results. Individual genotyping of HPV-16 or HPV-18, if present. Aids in triaging women with positive HR-HPV but negative Pap smear results.

Interpretation: Cytology: Standard reporting, as defined by the Bethesda System (TBS) is utilized. Human papillomavirus (HPV): A positive result indicates the presence of HPV DNA due to 1 or more of the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. A negative result indicates the absence of HPV DNA of the targeted genotypes. For patients with atypical squamous cells of undetermined significance (ASC-US) Pap smear result and who are positive for high-risk HPV (HR-HPV), consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear result but who are positive for HPV-16 or HPV-18, consider referral for colposcopy, if clinically indicated. For women aged 30 years and older with a negative Pap smear, positive HR-HPV test result, but who are negative for HPV-16 and HPV-18, consider repeat testing by both cytology and a HR-HPV test in 12 months.

Reference Values:
ThinPrep PAPANICOLAOU
Satisfactory for evaluation. Negative for intraepithelial lesion or malignancy.

**HUMAN PAPILLOMAVIRUS (HPV)**

Negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

**Clinical References:**

1. Lorincz AT, Richart RM: Human papillomavirus DNA testing as an adjunct to cytology in cervical screening programs. Arch Pathol Lab Med 2003 August;127(8):959-968

**FFTIO**

**Thiocyanate, serum**

**Reference Values:**

Toxic Thiocyanate concentrations: Greater than 10 mg/dL.

**TPMT3**

**Thiopurine Methyltransferase (TPMT) Activity Profile, Erythrocytes**

**Clinical Information:** Thiopurine methyltransferase (TPMT) deficiency is a condition in which patients treated with standard doses of azathioprine (AZA, Imuran), 6-mercaptopurine (6-MP, Purinethol), or 6-thioguanine (6-TG, Thioguanine Tabloid) may develop life-threatening myelosuppression or severe hematopoietic toxicity. The metabolic conversion of AZA, 6-MP, or 6-TG to purine nucleotides and the subsequent incorporation of these nucleotides into DNA play an important role in both the therapeutic efficacy and the toxicity of these drugs. A competitive catabolic route for the metabolism of thiopurines is catalyzed by the TPMT enzyme, which inactivates them by thiomethylation. A balance must be established between these competing metabolic pathways so that: 1) sufficient amounts of drug are converted to the nucleotide to act as an antimetabolite and 2) the antimetabolite levels do not become so high as to cause potentially lethal bone marrow suppression. TPMT deficiency is an autosomal recessive condition with an incidence of approximately 1 in 300 individuals homozygous for deleterious mutations in the TPMT gene; about 10% of the population are heterozygous carriers of TPMT mutations. Adverse effects of AZA, 6-MP, or 6-TG administration can be observed in individuals who are either homozygous or heterozygous for TPMT deficiency. TPMT hyperactivity is also a known phenotype. Individuals who are hypermetabolizers have therapeutic resistance to thiopurine drugs, and therefore they cannot achieve therapeutic levels. If an individual with TPMT hyperactivity is treated with higher and higher doses of thiopurine drugs, they may develop severe hepatotoxicity. Therefore, treatment with alternative medications is recommended for hypermetabolizers. As such, knowing a patient’s TPMT status prior to treatment with AZA, 6-MP, or 6-TG is important for purposes of calculating drug dosages.

**Useful For:** Detection of individuals with low thiopurine methyltransferase (TPMT) activity who are at risk for excessive myelosuppression or severe hematopoietic toxicity when taking thiopurine drugs
Detection of individuals with hyperactive TPMT activity who have therapeutic resistance to thiopurine drugs and may develop hepatotoxicity if treated with these drugs

**Interpretation:** This thiopurine methyltransferase (TPMT) activity profile RBC assay is used to detect individuals with low and intermediate TPMT activity who may be at risk for myelosuppression when exposed to standard doses of thiopurines, including azathioprine (AZA, Imuran), 6-mercaptopurine (Purinethol), or 6-thioguanine (6-TG, Thio guanine Tabloid). TPMT is the primary metabolic route for inactivation of thiopurine drugs in the bone marrow. When TPMT activity is low, it is predicted that proportionately more 6-mercaptopurine can be converted into the cytotoxic 6-thioguanine nucleotides that accumulate in the bone marrow causing excessive toxicity. This test can also detect TMPT hyperactivity. Individuals who are hypermetabolizers have therapeutic resistance to thiopurine drugs, and therefore they cannot achieve therapeutic levels. If an individual with TPMT hyperactivity is treated with higher and higher doses of thiopurine drugs, they may develop severe hepatotoxicity. The activity of TPMT is measured by 3 different substrates. Reports include the quantitative activity level of TPMT for each of 3 different substrates and an interpretation of these results. When abnormal results are detected, a detailed interpretation is given, including an overview of results and suggestion as to whether patient has TPMT deficiency or hyperactivity, as well as discussion of treatment considerations. TPMT phenotype testing does not replace the need for clinical monitoring of patients treated with thiopurine drugs. Genotype for TPMT cannot be inferred from TPMT activity (phenotype). Phenotype testing should not be requested for patients currently treated with thiopurine drugs. Thiopurine methyltransferase (TPMT) activity is measured in RBCs. If a patient has had a recent blood transfusion, within 30 to 60 days of testing, the patient's true enzyme activity may not be accurately reflected.

**Reference Values:**
- 3.00-6.66 nmol/mL/hour 6-Methyl mercaptopurine (normal)
- 5.04-9.57 nmol/mL/hour 6-Methyl mercaptopurine riboside (normal)
- 2.70-5.84 nmol/mL/hour 6-Methyl thioguanine riboside (normal)

**Clinical References:**

**TPNUV 65160**

**Thiopurine Methyltransferase (TPMT) and Nudix Hydrolase (NUDT15) Genotyping, Varies**

**Clinical Information:** The thiopurine drugs are purine antimetabolites that are useful in the treatment of acute lymphoblastic leukemia, autoimmune disorders (eg, Crohn disease, rheumatoid arthritis), and organ transplant recipients. The thiopurine drugs, 6-mercaptopurine (6-MP), 6-thioguanine (6-TG), and azathioprine (AZA) are prodrugs that require intracellular activation to 6-thioguanine nucleotides (6-TGN). This activation is catalyzed by multiple enzymes. The cytotoxic effects of thiopurine drugs are achieved mainly through incorporation of 6-TGN into DNA and RNA. The pathway that leads to synthesis of active cytotoxic 6-TGN is in competition with inactivation pathways catalyzed by thiopurine methyltransferase (TPMT). Evaluation of this pathway is important because the level of 6-TGN measured in red blood cells have been correlated with both thiopurine therapeutic efficacy and toxicity such as myelosuppression. TPMT activity is inherited as a monogenic codominant trait, and variable TPMT activity is associated with TPMT genetic variants. The distribution of TPMT activity in red blood cells is trimodal in Caucasians, with approximately 0.3% of people having deficient (undetectable) TPMT activity, 11% low (intermediate) activity, and 89% normal TPMT activity. The allele for normal TPMT activity (wild-type) has been designated TPMT*1. Four TPMT alleles, comprised of a combination of 3 different single-nucleotide substitutions (SNP), account for the majority of inactivating alleles in some ethnicities, including Caucasians: TPMT*2, TPMT*3A, TPMT*3B, and TPMT*3C. Less frequently
occurring TPMT alleles TPMT*4, TPMT*5, TPMT*8, and TPMT*12 also have been implicated as deficiency alleles. If no TPMT variant alleles are detected by this assay, the most likely genotype is that of TPMT*1/*1 although the presence of other rarer alleles cannot be excluded. Nudix hydrolase (NUDT15) is thought to dephosphorylate the active metabolites of thiopurines, TGTP and TdGTP, which prevents their incorporation into DNA and decreases their cytotoxic effects. Genetic variants in NUDT15 that decrease this activity are strongly associated with thiopurine-related myelosuppression. NUDT deficiency is most common among East Asians (22.6%), followed by South Asians (13.6%), and Native American populations (12.5%-21.2%). Studies in other populations are ongoing. This test evaluates variants associated with NUDT15*2, NUDT15*3, NUDT15*4, and NUDT15 *5. If no NUDT15 variant alleles are detected by this assay, the most likely genotype is that of NUDT15*1/*1 although the presence of other rarer alleles cannot be excluded. Individuals with variants in both TPMT and NUDT15 have been identified and were significantly more sensitive to mercaptopurine than individuals with variants in only 1 gene. Integration of both TPMT and NUDT15 testing may allow for more accurate prediction of thiopurine-related toxicity risk to guide dosing, particularly among patients from diverse populations.

### TPMT Allele cDNA Nucleotide Change Amino Acid Change Effect on Enzyme Metabolism

**TPMT Allele cDNA Nucleotide Change Amino Acid Change Effect on Enzyme Metabolism**

<table>
<thead>
<tr>
<th>Allele</th>
<th>cDNA Nucleotide Change</th>
<th>Amino Acid Change</th>
<th>Effect on Enzyme Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1</td>
<td>None (wild type)</td>
<td>None (wild type)</td>
<td>Normal function</td>
</tr>
<tr>
<td>*2</td>
<td>c.238G&gt;C p.Ala80Pro (p.A80P)</td>
<td>No activity</td>
<td></td>
</tr>
<tr>
<td>*3A</td>
<td>c.460G&gt;A and c.719A&gt;G p.Ala154Thr (p.A154T) and p.Tyr240Cys (p.Y240C)</td>
<td>No activity</td>
<td></td>
</tr>
<tr>
<td>*3B</td>
<td>c.460G&gt;A p.Ala154Thr (p.A154T)</td>
<td>No activity</td>
<td></td>
</tr>
<tr>
<td>*3C</td>
<td>c.719A&gt;G p.Tyr240Cys (p.Y240C)</td>
<td>No activity</td>
<td></td>
</tr>
<tr>
<td>*4</td>
<td>c.626-1G&gt;A</td>
<td>Not applicable, splice site</td>
<td>No activity</td>
</tr>
<tr>
<td>*5</td>
<td>c.146T&gt;C p.Leu49Ser (p.L49S)</td>
<td>No activity</td>
<td></td>
</tr>
<tr>
<td>*12</td>
<td>c.374C&gt;T p.Ser125Leu (p.S125L)</td>
<td>Reduced activity</td>
<td></td>
</tr>
</tbody>
</table>

The US Food and Drug Administration, the Clinical Pharmacogenetics Implementation Consortium, and some professional societies recommend consideration of TPMT genotype or TPMT erythrocyte testing prior to the initiation of therapy with thiopurine drugs. There is substantial evidence linking TPMT genotype to phenotypic variability. Dose adjustments based upon TPMT genotype have reduced thiopurine-induced adverse effects without compromising desired antitumor and immunosuppressive therapeutic effects in several clinical settings. Genotyping is not impacted by other medications known to inhibit TPMT activity. Complementary clinical testing is available to measure TPMT enzymatic activity in erythrocytes (TPMT3 / Thiopurine Methyltransferase (TPMT) Activity Profile, Erythrocytes) if the clinician wants to check for lower TPMT enzyme activity, regardless of cause. Although there currently aren't guidelines or professional society recommendations related to NUDT15 genotyping to guide thiopurine use, this practice is substantially supported by the literature. Testing for TPMT enzyme activity is not impacted by variants in NUDT15. NUDT15 Allele cDNA Nucleotide Change Amino Acid Change Effect on Enzyme Metabolism

### NUDT15 Allele cDNA Nucleotide Change Amino Acid Change Effect on Enzyme Metabolism

**NUDT15 Allele cDNA Nucleotide Change Amino Acid Change Effect on Enzyme Metabolism**

<table>
<thead>
<tr>
<th>Allele</th>
<th>cDNA Nucleotide Change</th>
<th>Amino Acid Change</th>
<th>Effect on Enzyme Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1</td>
<td>None (wild type)</td>
<td>None (wild type)</td>
<td>Normal activity</td>
</tr>
<tr>
<td>*2</td>
<td>c.415C&gt;T p.Arg139Cys (p.R139C)</td>
<td>No activity</td>
<td></td>
</tr>
<tr>
<td>*4</td>
<td>c.416G&gt;A p.Arg139His (p.R139H)</td>
<td>No activity</td>
<td></td>
</tr>
<tr>
<td>*5</td>
<td>c.52G&gt;A p.Val18Ile (p.V18I)</td>
<td>No activity</td>
<td></td>
</tr>
</tbody>
</table>

**Useful For:** Predicting potential for toxicity to thiopurine drugs (6-mercaptopurine, 6-thioguanine, and azathioprine)

**Interpretation:** An interpretive report will be provided. The TPMT genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by the TPMT Nomenclature Committee. (1) NUDT15 genotype and associated star alleles are as described by Moriyama et al. (2) For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomics Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:** An interpretive report is provided.

**Clinical References:**
1. TPMT nomenclature committee. Available at www.imh.liu.se/tpmtalleles
**Thiosulfate, Urine**

**Reference Values:**
Reporting limit determined each analysis

Creatinine (mg/L)
- U.S. Population (10th â€“ 90th percentiles, median)
  - All participants: 335 - 2370 mg/L, median: 1180 (n=22,245)
  - Males: 495 - 2540 mg/L, median: 1370 (n=10,610)
  - Females: 273 - 2170 mg/L, median 994 (n=11,635)

Thiosulfate (mcg/mL)
- Normal range: approximately 2.9 +/- 2.5 mcg/mL (based on an average creatinine concentration of 1 g/L)

Thiosulfate (Creatinine corrected) (mg/g Creat)
- Thiosulfate was detected in urine from 29 controls at 2.9 +/- 2.5 mg/g creatinine.
- Exposure to 1240 nmol/L (30 ppm) for 45 minutes resulted in a urinary thiosulfate concentration of 60 mg/g creatinine.

Specific Gravity Confirmation
- Physiologic range: 1.010 - 1.030.

**Thiothixene (Navane)**

**Reference Values:**
Reference Range: 10.0 - 30.0 ng/mL

**Thrombin Time (Bovine), Plasma**

**Clinical Information:** Prolonged clotting times may be associated with a wide variety of coagulation abnormalities including: -Deficiency or functional abnormality (congenital or acquired) of many of the coagulation proteins -Deficiency or functional abnormality of platelets -Specific factor inhibitors -Acute disseminated intravascular coagulation -Exogenous anticoagulants (eg, heparin, warfarin) The prothrombin time and activated partial thromboplastin time are first-order tests for coagulation abnormalities and are prolonged in many disorders. A battery of coagulation tests is often required to determine the cause of prolonged clotting times. Thrombin catalyzes the transformation of fibrinogen to fibrin (by cleaving fibrinopeptides A and B), which is followed by polymerization of fibrin to form a clot. The thrombin time (TT) test measures the time of clot formation when thrombin is added to citrated plasma. The phospholipid-dependent procoagulant enzyme cascades (intrinsic, extrinsic, and "common" pathway) are bypassed by the addition of exogenous thrombin. Therefore, the TT mainly reflects functions and interactions of solution-phase exogenous thrombin and endogenous fibrinogen.

**Useful For:** The main utility of the thrombin time test is to detect or exclude the presence of heparin or heparin-like anticoagulants (which act by enhancing antithrombin's inhibition of thrombin and other procoagulant enzymes) when used in conjunction with the reptilase time (RT) in evaluating unexplained prolonged clotting times. Identifying the cause of a prolonged prothrombin time, activated partial thromboplastin time, or dilute Russell's viper venom time when used in conjunction with the RT and fibrinogen assay
**Interpretation:** Prolongation of the thrombin time (TT) is consistent with the presence of heparin-like anticoagulants, hypofibrinogenemia, dysfibrinogenemia, fibrin degradation products, and antibody inhibitors of thrombin. An immeasurably prolonged TT is usually the result of heparin in the specimen or, rarely, the presence of thrombin antibodies or afibrinogenemia. When the TT test is performed with diluted bovine thrombin to achieve a normal plasma clotting time of about 20 seconds, the TT is capable of detecting unfractionated heparin at a concentration of 0.05 units/mL of heparin. Other tests useful in interpreting the significance of prolongation of the TT include: reptilase time (RT), human thrombin time, clottable fibrinogen assay, and the fibrin D-dimer assay. These tests are available as components of coagulation profile test panels. As seen in the following table, RT can help distinguish among the various causes of a prolonged TT.

**Thrombin Time Reptilase Time Causes Remarks**

<table>
<thead>
<tr>
<th>Prolonged</th>
<th>Prolonged</th>
<th>Hypo- or afibrinogenemia Ascertain by determination of fibrinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Dysfibrinogenemia Ascertain by specific assay</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Normal</td>
<td>Heparin or inhibitor of thrombin Differentiate by human TT and/or heparin assays</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Fibrin(ogen) split products (FSP) Ascertain by FSP or D-dimer assay</td>
</tr>
</tbody>
</table>

**Reference Values:**
15-23 seconds

**Clinical References:**

**FFTAT 91200**

**Thrombin-Antithrombin Complex**

**Reference Values:**
<4.3 ng/mL

Pre-analytical conditions such as a difficult draw may spuriously increase test results.

**THRMP 83093**

**Thrombophilia Profile**

**Clinical Information:** Thrombophilia is defined as an acquired or familial disorder associated with thrombosis. The clinical presentation of an underlying thrombophilia predominantly includes venous thromboembolism (deep vein thrombosis, pulmonary embolism, superficial vein thrombosis). Other manifestations that have been linked to thrombophilia include recurrent miscarriage and complications of pregnancy (eg, severe preeclampsia, abruptio placenta, intrauterine growth restriction, stillbirth). The current thrombophilia does not predict for arterial thrombosis. Demographic or environmental exposures that compound the risk of venous thromboembolism among persons with a thrombophilia include increasing age, male gender, obesity, surgery, trauma, hospitalization for medical illness, malignant neoplasm, prolonged immobility during travel (eg, prolonged airplane travel), oral contraceptive use, estrogen therapy (both oral and transdermal), tamoxifen and raloxifene therapy, and infertility drugs. Central venous catheters and transvenous pacemaker wires increase the risk for upper extremity deep vein thrombosis; this risk is unrelated to thrombophilia. Inherited thrombophilias include: -Deficiency due to reduced plasma protein level or dysfunctional protein of:  -Antithrombin  -Protein C  -Protein S  -Dysfibrinogenemias (rare)  -Activated protein C resistance due to the factor V R506Q (Leiden) mutation -Prothrombin G20210A mutation Acquired thrombophilias include a lupus-like anticoagulant (antiphospholipid antibodies) and disseminated intravascular coagulation/intravascular coagulation and fibrinolysis (DIC/ICF). DIC/ICF may cause thrombotic as well as hemorrhagic events. Positive tests for DIC/ICF can also occur as consequences of thrombosis. Acquired deficiencies of fibrinogen, protein C, protein S, and antithrombin may be found in conjunction with liver disease (they are produced by the liver) or DIC/ICF and are of uncertain significance with respect to thrombosis risk. Acquired deficiencies of protein C and protein S are also found in patients with HIV infection.
with liver disease who are being treated with oral anticoagulants (eg, warfarin, Coumadin), since both of these proteins are dependent upon the action of vitamin K for normal function. Acquired protein S deficiency also occurs in thrombotic thrombocytopenic purpura, pregnancy or estrogen therapy, nephrotic syndrome, and sickle cell anemia. In acute illness, the level of acute-phase reactants rise (including C4b binding protein, which binds and inactivates protein S in the plasma) and the portion of bound protein S also rises leaving a lower proportion of free protein S. The significance of acquired protein S deficiency with respect to thrombosis risk is unknown.

**Useful For:** Evaluating patients with thrombosis or hypercoagulability states Detecting a lupus-like anticoagulant; dysfibrinogenemia; disseminated intravascular coagulation/intravascular coagulation and fibrinolysis Detecting a deficiency of antithrombin, protein C, or protein S Detecting activated protein C resistance (and the factor V R506Q [Leiden] mutation if indicated) Detecting the prothrombin G20210A mutation

**Interpretation:** An interpretive report will be provided.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FFTP0 57822**
**Thrombopoietin (TPO)**

**Reference Values:**
7 â€“ 99 pg/mL

**THYM 82606**
**Thyme, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive

Reference values apply to all ages.


TGAB
84382

Thyroglobulin Antibody, Serum

Clinical Information: Thyroglobulin autoantibodies bind thyroglobulin (Tg), a major thyroid-specific protein. Tg plays a crucial role in thyroid hormone synthesis, storage, and release. Tg is not secreted into the systemic circulation under normal circumstances. However, follicular destruction through inflammation (thyroiditis and autoimmune hypothyroidism), hemorrhage (nodular goiter), or rapid disordered growth of thyroid tissue, as may be observed in Graves disease or follicular cell-derived thyroid neoplasms, can result in leakage of Tg into the blood stream. This results in the formation of autoantibodies to Tg (anti-Tg) in some individuals. The same processes also may result in exposure of other “hidden” thyroid antigens to the immune system, resulting in the formation of autoantibodies to other thyroid antigens, in particular thyroid peroxidase (TPO) (anti-TPO). Since anti-Tg and anti-TPO autoantibodies are observed most frequently in autoimmune thyroiditis (Hashimoto disease), they were originally considered to be of possible pathogenic significance in this disorder. However, the consensus opinion today is that they are merely disease markers. It is felt that the presence of competent immune cells at the site of thyroid tissue destruction in autoimmune thyroiditis simply predisposes the patient to form autoantibodies to hidden thyroid antigens. In individuals with autoimmune hypothyroidism, 30% to 50% will have detectable anti-Tg autoantibodies, while 50% to 90% will have detectable anti-TPO autoantibodies. In Graves disease, both types of autoantibodies are observed at approximately half these rates. The presence of anti-Tg, which occurs in 15% to 30% of thyroid cancer patients, could result in misleading Tg results. In immunometric assays, the presence of thyroid antibody can lead to false-low measurement; whereas it might lead to false-high results in competitive assays.

Useful For: As an adjunct in the diagnosis of autoimmune thyroid diseases: Hashimoto disease, postpartum thyroiditis, neonatal hypothyroidism, and Graves disease Identification of potentially unreliable serum thyroglobulin measurements by immunoassay in the follow-up of patients with differentiated follicular-cell derived thyroid carcinomas (for this application order HTG2 / Thyroglobulin, Tumor Marker, Serum or HTGR / Thyroglobulin, Tumor Marker Reflex to LC-MS/MS or Immunoassay)

Interpretation: Diagnosis of Autoimmune Thyroid Disease: Measurements of antithyroid peroxidase (TPO) have higher sensitivity and equal specificity to antithyroglobulin (anti-Tg) measurements in the diagnosis of autoimmune thyroid disease. Anti-Tg levels should, therefore, only be measured if anti-TPO measurements are negative, but clinical suspicion of autoimmune thyroid disease is high. Detection of significant titers of anti-Tg or anti-TPO autoantibodies is supportive evidence for a diagnosis of Graves disease in patients with thyrotoxicosis. However, measurement of the pathogenic antithyroid-stimulating hormone (TSH) receptor antibodies by binding assay (THYRO / Thyrotropin Receptor Antibody, Serum) or bioassay (TSI / Thyroid-Stimulating Immunoglobulin [TSI], Serum) is the preferred method of confirming Graves disease in atypical cases and under special clinical conditions.
circumstances. Positive thyroid autoantibody levels in patients with high-normal or slightly elevated serum thyrotropin levels predict the future development of more profound hypothyroidism. Patients with postpartum thyroiditis with persistently elevated thyroid autoantibody levels have an increased likelihood of permanent hypothyroidism. In cases of neonatal hypothyroidism, the detection of anti-TPO or anti-Tg in the infant suggests transplacental antibody transfer, particularly if the mother has a history of autoimmune thyroiditis or detectable thyroid autoantibodies. The neonatal hypothyroidism is likely to be transient in these cases. Thyroid Cancer Follow-up: Following therapy of differentiated follicular-cell derived thyroid cancer, patients with no residual thyroid tissue and no persistent or recurrent cancer will have undetectable or very low serum Tg levels. Persistently elevated or rising serum Tg levels, either on or off thyroxine replacement therapy, suggest possible tumor persistence or recurrence. However, if a patient also has measurable anti-Tg autoantibody levels, the results of serum Tg measurements may be unreliable. Anti-Tg may result in both falsely-low and, less commonly, falsely high serum Tg measurements. Therefore, in anti-Tg-positive patients, serum Tg measurements should not be used as the sole measurement for thyroid cancer follow-up and should be interpreted with caution. A thyroglobulin antibody result of <4.0 IU/mL is unlikely to cause clinically significant thyroglobulin assay interference. It is recommended that the thyroglobulin result be reviewed for concordance with clinical presentation.

Reference Values:

<4.0 IU/mL

Reference values apply to all ages.


Thyroglobulin Immunostain, Technical Component Only

Clinical Information: Thyroglobulin is a glycoprotein product of thyroid epithelial cells, which is then complexed with iodine before being secreted as thyroid hormone in the blood. In normal thyroid, thyroglobulin staining is seen at the apical surface of thyrocytes and within the colloid in the center of thyroid follicles. The thyroglobulin antibody is useful in classifying poorly differentiated or metastatic thyroid carcinomas.

Useful For: Classification of thyroid carcinoma

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Thyroglobulin Mass Spectrometry, Serum

Clinical Information: Thyroglobulin (Tg) is a highly thyroid-specific large homodimeric glycoprotein (approximately 660 KDa). It contains 8% to 10% of carbohydrates and iodine. Thyroxine (T4) and triiodothyronine (T3) are synthesized on Tg within the lumen of thyroid follicles. For T4 and T3 release, Tg is reabsorbed into thyrocytes and proteolytically degraded, liberating T4 and T3 for secretion. Small amounts of intact Tg are secreted alongside T4 and T3 and are detectable in the serum of healthy individuals, with levels roughly paralleling thyroid size (0.5-1.0 ng/mL per gram thyroid tissue, depending on thyroid-stimulating hormone [TSH] level). In situations of disordered thyroid growth (eg, goiter), increased thyroid activity (eg, Graves’ disease), or glandular destruction (eg, thyroiditis), larger amounts of Tg may be released into the circulation. Clinically, the main use of serum Tg measurements is in the follow-up of differentiated follicular cell-derived thyroid carcinoma. Because Tg is highly organ-specific, serum Tg concentrations should be undetectable, or very low, after the thyroid gland is removed during primary treatment for thyroid cancer. Current clinical guidelines consider a serum Tg of >1 ng/mL in an athyrotic individual as suspicious of possible residual or recurrent disease. To improve diagnostic accuracy, it is recommended that at least initially this measurement is obtained after TSH stimulation, either following thyroid hormone withdrawal, or after injection of recombinant human TSH. Most patients will have a relatively low risk of recurrence, and will thereafter only require unstimulated Tg measurement. If unstimulated (on thyroxine) serum Tg measurements are <0.1 to 0.2 ng/mL, the risk of disease is <1%. Patients with higher Tg levels, who have no demonstrable remnant of thyroid tissue, might require additional testing, such as further stimulated Tg measurements, neck ultrasound, or isotope imaging. A stimulated Tg >2 ng/mL is considered suspicious. There are 3 situations, when serum Tg measurement might be misleading: 1. Remnant thyroid tissue (see above, 0.5-1 ng/mL Tg per gram) 2. Antithyroglobulin autoantibodies (TgAB), which occur in 15% to 30% of thyroid cancer patients, can lead to false-low measurement in immunometric assays (most commonly used); in competitive assays they may cause false-high results. 3. Heterophile antibodies (HAB) are antibodies that are capable of interacting with the antibodies used in immunoassays, usually resulting in false-high measurements. Depending on the assay and the patient population, this can lead to erroneously high results in 0.1% to 3.0% of patients. Traditionally, there have been no reliable means to obtain accurate Tg measurements in patients with TgAB or HAB. However, recently, trypsin digestion of serum proteins, which cuts both antibodies and Tg into predictable fragments, has allowed accurate quantification of Tg in samples with antibody interferences through measurement of Tg-specific tryptic peptides by mass spectrometry.

Useful For: Accurate measurement of serum thyroglobulin (Tg) in patients with known or suspected antithyroglobulin autoantibodies (TgAB) or heterophile antibodies (HAB) Reflex testing of samples with previously unknown TgAB status that prove TgAB positive during immunoassay testing Rarely, in patients without thyroid cancer to assist in the differential diagnosis of early phase silent thyroiditis versus Graves’ disease (the mass spectrometry-based method would only be required if these patients have TgAB or HAB)

Interpretation: Current guidelines recommend measurement of thyroglobulin (Tg) with a sensitive immunoassay limit of quantification <1 ng/mL; for measurements of unstimulated Tg, the detection limit should be in the 0.1 to 0.2 ng/mL range. In all cases, serum antithyroglobulin autoantibodies (TgAB) should also be measured, preferably with a method that allows detection of low concentrations of TgAB (< or =20 kIU/L). If TgAB are detected, the laboratory report should alert the ordering provider to the possibility of false-low Tg results. If the apparent Tg concentration is <1 ng/mL, the sample should be remeasured by mass spectrometry. This will allow confident detection of Tg in the presence of TgAB down to 0.5 ng/mL (risk of residual/recurrent disease <1-3%). Samples from patients with Tg concentrations >1 ng/mL (or 2 ng/mL; there is some discussion in the literature) might not require Tg measurement by mass spectrometry, because current guidelines suggest further work-up might be necessary above this threshold. However the positive predictive value for residual/recurrent disease is modest at best when Tg is just above this threshold (3%-25%, rising in parallel with Tg concentrations up to 10 ng/mL) in athyrotic patients. Above 10 ng/mL, the risk of residual/recurrent disease is at least 25%, with many studies showing 60% to >90% risks. In selected patients, it might therefore also be useful to test TgAB positive samples by mass spectrometry, even if the Tg
concentration is >1.0 ng/mL, but has not yet passed the 10 ng/mL threshold. These considerations are even more relevant in patients with a known thyroid remnant of a few grams, who may always have serum Tg concentrations of 1.0 to 10 ng/mL, owing to remnant Tg secretion, regardless of the presence or absence of residual/recurrent cancer. There are no routine tests that can detect heterophile antibodies in patient samples. An unexpected high result is usually the tip-off in this case, and should prompt remeasurement by mass spectrometry, which will provide a reliable result. It has been determined that the presence of Tg autoantibodies in serum can lead to underestimation of Tg concentration by immunoassay methods. When antibodies are present in samples with detectable Tg, the Tg values may be underestimated by up to 60% in immunoassays. In addition, 20% of specimens containing antibodies that are negative for Tg by immunoassay tested positive by liquid chromatography-tandem mass spectrometry (LC-MS/MS); no results over 3 ng/mL by LC-MS/MS were observed. In rare cases, when Tg is measured in patients with an intact thyroid gland who do not have thyroid cancer, substantial elevations will primarily be observed in very large goiters, highly active Graves disease, and, most pronounced, in the early phase of acute thyroiditis, when follicular destruction releases massive amounts of stored Tg into the circulation. Levels are often well above 100 ng/mL.

**Reference Values:**

Healthy individuals with intact, functioning thyroid: < or =33 ng/mL

The reference ranges listed below, however, are for thyroid cancer follow up of athyrotic patients and apply to unstimulated and stimulated thyroglobulin measurements. Ranges are based on best practice guidelines and the literature, which includes Mayo Clinic studies, and represent clinical decision levels.

Decision levels for thyroid cancer patients, who are not completely athyrotic (ie, patient has some remnant normal thyroid tissue), have not been established, but are likely to be somewhat higher: remnant normal thyroid tissue contributes to serum Tg concentrations 0.5-1.0 ng/mL per gram of remnant tissue, depending on the thyroid-stimulating hormone (TSH) level.

Tg <0.5 ng/mL: Thyroglobulin (Tg) levels must be interpreted in the context of TSH levels, serial Tg measurements, and radioiodine ablation status. Undetectable Tg levels in athyrotic individuals on suppression therapy indicate a minimal risk (<1%-2%) of clinically detectable recurrent papillary/follicular thyroid cancer.

Tg > or =0.5 ng/mL to 2.0 ng/mL: Thyroglobulin (Tg) levels must be interpreted in the context of TSH levels, serial Tg measurements, and radioiodine ablation status. Tg levels of 0.5-2.0 ng/mL in athyrotic individuals on suppressive therapy indicate a low risk of clinically detectable recurrent papillary/follicular thyroid cancer.

Tg 2.1 ng/mL to 9.9 ng/mL: Thyroglobulin (Tg) levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels of 2.1-9.9 ng/mL in athyrotic individuals on suppression therapy indicate an increased risk of clinically detectable recurrent papillary/follicular thyroid cancer.

Tg > or =10 ng/mL: Thyroglobulin (Tg) levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels of > or =10 ng/mL in athyrotic individuals on suppressive therapy indicate a significant (>25%) risk of clinically detectable recurrent papillary/follicular thyroid cancer.

**Clinical Information:** Thyroglobulin (Tg) is a thyroid-specific glycoprotein (approximately 660 KDa) that serves as the source for thyroxine (T4) and triiodothyronine (T3) production within the lumen of thyroid follicles. For T4 and T3 release, Tg is reabsorbed into thyrocytes and proteolytically degraded, liberating T4 and T3 for secretion. Small amounts of intact Tg are secreted alongside T4 and T3 and are detectable in the serum of healthy individuals, with levels roughly paralleling thyroid size (0.5-1.0 ng/mL Tg per gram thyroid tissue, depending on thyroid-stimulating hormone [TSH] level). In situations of disordered thyroid growth (eg, goiter), increased thyroid activity (eg, Graves' disease), or glandular destruction (eg, thyroiditis) larger amounts of Tg may be released into the circulation. Clinically, the main use of serum Tg measurements is in the follow-up of differentiated follicular cell-derived thyroid carcinoma. Because Tg is thyroid-specific, serum Tg concentrations should be undetectable, or very low, after the thyroid gland is removed during treatment for thyroid cancer. Current clinical guidelines consider a serum Tg of >1 ng/mL in an athyrotic individual as suspicious of possible residual or recurrent disease. To improve diagnostic accuracy, it is recommended that at least initially this measurement is obtained after thyroid stimulating hormone (TSH) stimulation, either following thyroid hormone withdrawal, or after injection of recombinant human TSH. Most patients will have a relatively low risk of recurrence, and will thereafter only require unstimulated Tg measurement. If unstimulated (on thyroxine) serum Tg measurements are <0.1 to 0.2 ng/mL, the risk of disease is <1%. Patients with higher Tg levels, who have no demonstrable remnant of thyroid tissue, might require additional testing, such as further stimulated Tg measurements, neck ultrasound, or isotope imaging. A stimulated Tg >2 ng/mL is considered suspicious. The presence of anti-thyroglobulin autoantibodies (TgAb), which occur in 15% to 30% of thyroid cancer patients, could lead to misleading Tg results. In immunometric assays, the presence of TgAb can lead to false low measurement; whereas it might lead to false high results in competitive assays. Traditionally, there have been no reliable means to obtain accurate Tg measurements in patients with TgAb. However, recently, trypsin digestion of serum proteins, which cuts both antibodies and Tg into predictable fragments, has allowed accurate quantification of Tg in samples with antibody interferences through measurement of Tg-specific tryptic peptides by mass spectrometry.

**Useful For:** Reporting of accurate thyroglobulin results, depending on the anti-thyroglobulin antibodies status of the patient. Accurate measurement of serum thyroglobulin in patients with known or suspected anti-thyroglobulin autoantibodies or possible heterophile antibodies.

**Interpretation:** Current guidelines recommend measurement of thyroglobulin (Tg) with a sensitive immunoassay - limit of quantification <1 ng/mL; for measurements of unstimulated Tg, the detection limit should be in the 0.1 to 0.2 ng/mL range. In all cases, serum anti-thyroglobulin autoantibodies (TgAb) should also be measured, preferably with a method that allows detection of low concentrations of TgAb. If TgAb are detected, the laboratory report should alert the ordering provider to the possibility of false-low Tg results. If the apparent Tg concentration is <1.0 ng/mL, the sample should be remeasured by mass spectrometry. This will allow confident detection of Tg in the presence of TgAb down to 0.5 ng/mL (risk of residual/recurrent disease <1%-3%). Samples from patients with Tg concentrations >1.0 ng/mL might not require Tg measurement by mass spectrometry, because current guidelines suggest further work-up might be necessary above this threshold. However the positive predictive value for residual/recurrent disease is modest when Tg is just above this threshold (3%-25%) in athyrotic patients. Above 10 ng/mL, the risk of residual/recurrent disease is at least 25%, with many studies showing 60% to >90% risks. In selected patients, it might therefore also be useful to test TgAb positive samples by mass spectrometry, even if the Tg concentration is >1.0 ng/mL, but has not yet passed the 10 ng/mL threshold. These considerations are even more relevant in patients with a known thyroid remnant of a few grams, who may always have serum Tg concentrations of 1.0 to 10 ng/mL, owing to remnant Tg secretion, regardless of the presence or absence of residual/recurrent cancer. It has been determined that the presence of anti-thyroglobulin autoantibodies (TgAb), in serum can lead to underestimation of Tg concentration by immunometric methods. When TgAb are present in samples with detectable Tg, the Tg values may be underestimated by up to 60% in immunoassays. In addition, some specimens containing TgAb which are negative for Tg by immunoassay tested positive by LC-MS/MS. Therefore, measuring of Tg by mass spectrometry is the preferred method in TgAb.
positive patients. The listed decision levels, are for thyroid cancer follow-up of athyrotic patients and apply to unstimulated and stimulated thyroglobulin measurements. Decision levels are based on best practice guidelines and the literature, which includes Mayo Clinic studies. Decision levels for thyroid cancer patients, who are not completely athyrotic (ie, patient has some remnant normal thyroid tissue), have not been established, but are likely to be somewhat higher: remnant normal thyroid tissue contributes to serum Tg concentrations 0.5 to 1.0 ng/mL per gram of remnant tissue, depending on the thyroid-stimulating hormone (TSH) level. Thyroglobulin by Mass Spectrometry Tg <0.5 ng/mL: Thyroglobulin (Tg) levels must be interpreted in the context of thyroid-stimulating hormone (TSH) levels, serial Tg measurements, and radioiodine ablation status. Undetectable Tg levels in athyrotic individuals on suppression therapy indicate a minimal risk (<1%-2%) of clinically detectable recurrent papillary/follicular thyroid cancer. Tg > or =0.5 ng/mL to 2.0 ng/mL: Thyroglobulin (Tg) levels must be interpreted in the context of TSH levels, serial Tg measurements, and radioiodine ablation status. Tg levels of 0.5-2.0 ng/mL in athyrotic individuals on suppressive therapy indicate a low risk of clinically detectable recurrent papillary/follicular thyroid cancer. Tg 2.1 ng/mL to 9.9 ng/mL: Thyroglobulin (Tg) levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels of 2.1-9.9 ng/mL in athyrotic individuals on suppression therapy indicate an increased risk of clinically detectable recurrent papillary/follicular thyroid cancer. Tg > or =10 ng/mL: Thyroglobulin (Tg) levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels of > or =10 ng/mL in athyrotic individuals on suppressive therapy indicate a significant (>25%) risk of clinically detectable recurrent papillary/follicular thyroid cancer. Thyroglobulin by Immunoassay Tg <0.1 ng/mL: Thyroglobulin levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels <0.1 ng/mL in athyrotic individuals on suppressive therapy indicate a minimal risk (<1%-2%) of clinically detectable recurrent papillary/follicular thyroid cancer. Tg > or =0.1 to 2.0 ng/mL: Thyroglobulin levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels 0.1 to 2.0 ng/mL in athyrotic individuals on suppressive therapy indicate a low risk of clinically detectable recurrent papillary/follicular thyroid cancer. Tg 2.1 ng/mL to 9.9 ng/mL: Thyroglobulin levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels 2.1 to 9.9 ng/mL in athyrotic individuals on suppressive therapy indicate an increased risk of clinically detectable recurrent papillary/follicular thyroid cancer. Tg > or =10 ng/mL: Thyroglobulin levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels > or =10 ng/mL in athyrotic individuals on suppressive therapy indicate a significant risk (>25%) of clinically detectable recurrent papillary/follicular thyroid cancer.

Reference Values:
Thyroglobulin Antibody: <4.0 IU/mL


Thyroglobulin, Tumor Marker, Fine-Needle Aspiration (FNA)-Needle Wash, Lymph Node

Clinical Information: Thyroglobulin (Tg) is a 660,000 molecular weight glycoprotein produced exclusively by the follicular cells of the thyroid. It is secreted into the follicular lumen, where it serves as the precursor of, and storage reservoir for, thyroxine (T4) and triiodothyronine (T3). T4 and T3 are released after Tg is endocytosed and proteolytically degraded in the thyrocyte. Since Tg is produced only by follicular thyrocyte-derived cells, measurement of serum Tg levels in athyrotic patients enables detection of persistence, recurrence, or metastasis of differentiated thyroid carcinoma. In addition, because of the thyroid specificity of Tg, its measurement in biopsy specimens of nonthyroidal tissues may
assist in confirming and localizing metastatic disease. In the most common type of thyroid cancer, papillary thyroid carcinoma (PTC)—greater than 80% of all thyroid cancer cases, most metastatic disease occurs in loco-regional lymph nodes in the neck, which are easily examined by ultrasound. Most suspicious nodes undergo ultrasonography-guided fine-needle aspiration (FNA) cytology to determine a diagnosis. Unfortunately, in up to 20% of the specimens, inadequate cellularity or nonrepresentative sampling precludes the diagnosis. Several studies have reported that the detection of Tg in fine-needle aspiration (FNA)-needle washes improves the evaluation of suspicious lymph nodes in patients with differentiated thyroid carcinoma.(1-3) A recent study reported that a Tg cutoff of 1 ng/mL for FNA-needle wash specimens provided 100% sensitivity and 96.2% specificity for the detection of metastatic thyroid carcinoma in lymph nodes.(3) The diagnostic performance of needle wash Tg at the 1-ng/mL cutoff compared favorably with cytology (95.1% overall agreement) and allowed accurate diagnosis in 18 of the 19 cases in which cytology was nondiagnostic or not performed.(3) Additionally, when measuring Tg in FNA-needle wash specimens, the clinical performance of FNA Tg is unaffected by the presence of Tg antibodies, a frequent problem when measuring Tg levels in serum. Cytologic examination and measurement of Tg can be performed on the same specimen. To measure Tg, the FNA needle is rinsed with a small volume of normal saline solution immediately after a specimen for cytological examination has been expelled from the needle for a smear or CytoTrap preparation. Tg levels are measured in the needle wash.

**Useful For:** An adjunct to cytologic examination of fine-needle aspiration specimens in athyrotic individuals treated for differentiated thyroid cancer, to confirm or exclude metastases in enlarged or ultrasonographically suspicious lymph nodes

**Interpretation:** In athyrotic patients with a history of differentiated thyroid carcinoma, a fine-needle aspiration thyroglobulin (FNA-Tg) value greater than 1.0 ng/mL suggests the presence of metastatic follicular cell-derived thyroid carcinoma in the biopsied area. FNA-Tg measurements yield reliable results in most cases with nondiagnostic cytology, and are approximately equal in diagnostic accuracy to cytological examinations that are deemed sufficient for diagnosis.

**Reference Values:**

<table>
<thead>
<tr>
<th>Tg value</th>
<th>Clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; or =1.0 ng/mL</td>
<td>This cutoff has been validated for total needle wash volumes of &lt; or =1.5 mL of normal saline. If wash volumes are substantially larger, a lower cutoff might apply.</td>
</tr>
</tbody>
</table>

**Clinical References:**


**Thyroglobulin, Tumor Marker, Serum**

**Clinical Information:** Thyroglobulin (Tg) is a thyroid-specific glycoprotein (approximately 660 KDa) that serves as the source for thyroxine (T4) and triiodothyronine (T3) production within the lumen of thyroid follicles. For T4 and T3 release, Tg is reabsorbed into thyrocytes and proteolytically degraded, liberating T4 and T3 for secretion. Small amounts of intact Tg are secreted alongside T4 and T3 and are detectable in the serum of healthy individuals, with levels roughly paralleling thyroid size (0.5-1.0 ng/mL Tg per gram thyroid tissue, depending on thyroid-stimulating hormone: TSH level). In situations of disordered thyroid growth (eg, goiter), increased thyroid activity (eg, Grave disease), or glandular destruction (eg, thyroiditis) larger amounts of Tg may be released into the circulation. Clinically, the main use of serum Tg measurements is in the follow-up of differentiated follicular cell-derived thyroid carcinoma. Because Tg is thyroid-specific, serum Tg concentrations should be undetectable, or very low, after the thyroid gland is removed during treatment for thyroid cancer. Current clinical guidelines consider a serum Tg of >1 ng/mL in an athyrotic individual as suspicious of possible residual or recurrent disease. To improve diagnostic accuracy, it is recommended that at least initially this measurement is obtained after TSH stimulation, either following thyroid hormone
withdrawing, or after injection of recombinant human TSH. Most patients will have a relatively low risk of recurrence, and will thereafter only require unstimulated Tg measurement. If unstimulated (on thyroxine) serum Tg measurements are <0.1 to 0.2 ng/mL, the risk of disease is <1%. Patients with higher Tg levels, who have no demonstrable remnant of thyroid tissue, might require additional testing, such as further stimulated Tg measurements, neck ultrasound, or isotope imaging. A stimulated Tg >2 ng/mL is considered suspicious. The presence of antithyroglobulin autoantibodies (TgAb), which occur in 15% to 30% of thyroid cancer patients, could lead to misleading Tg results. In immunometric assays, the presence of TgAb can lead to false-low results; whereas it might lead to false-high results in competitive assays. Traditionally, there have been no reliable means to obtain accurate Tg measurements in patients with TgAb. However, recently, trypsin digestion of serum proteins, which cuts both antibodies and Tg into predictable fragments, has allowed accurate quantification of Tg in samples with antibody interferences through measurement of Tg- by mass spectrometry. Refer to TGMS / Thyroglobulin Mass Spectrometry, Serum for accurate sample analysis of patients who are known to be TgAb positive. If TgAb status is unknown, refer to HTGR / Thyroglobulin, Tumor Marker Reflex to LC-MS/MS or Immunoassay. When HTGR is ordered, TgAb testing is performed first. If TgAb is negative (<4.0 IU/mL), Tg is assayed by immunoassay (sensitive down to 0.1 ng/mL). If TgAb is positive, Tg is assayed by mass spectrometry (sensitive down to 0.5 ng/mL).

**Useful For:** Follow-up of patients with differentiated thyroid cancers after thyroidectomy and radioactive iodine ablation

**Interpretation:** Current guidelines recommend measurement of thyroglobulin (Tg) with a sensitive immunoassay (limit of quantification <1.0 ng/mL); for measurements of unstimulated Tg, the detection limit should be in the 0.1 to 0.2 ng/mL range. In all cases, serum thyroglobulin autoantibodies (TgAb) should also be measured, preferably with a method that allows detection of low concentrations of TgAb. If TgAb are detected, the laboratory report should alert the ordering provider to the possibility of false-low Tg results if using an immunometric assay. If the apparent Tg concentration is <1.0 ng/mL, the sample should be remeasured by mass spectrometry. This will allow accurate detection of Tg, in the presence of TgAb, down to 0.5 ng/mL (risk of residual/recurrent disease <1%-3%). Samples from patients with Tg concentrations >1.0 ng/mL might not require Tg measurement by mass spectrometry, because current guidelines suggest further workup might be necessary above this threshold. However the positive predictive value for residual/recurrent disease is modest when Tg is just above this threshold (3%-25%) in athyrotic patients. Above 10 ng/mL, the risk of residual/recurrent disease is at least 25%, with many studies showing 60% to >90% risks. In selected patients, therefore, it might also be useful to test TgAb positive samples by mass spectrometry, even if the Tg concentration is >1.0 ng/mL, but not above the 10 ng/mL threshold. These considerations are even more relevant in patients with a known thyroid remnant of a few grams, who may always have serum Tg concentrations of 1.0 to 10 ng/mL, owing to remnant Tg secretion, regardless of the presence or absence of residual/recurrent cancer. It has been determined that the presence of antithyroglobulin autoantibodies (TgAb), in serum can lead to underestimation of Tg concentration by immunometric methods. When TgAb are present in samples with detectable Tg, the Tg values may be underestimated by up to 60% in immunoassays. In addition, approximately 20% of specimens containing TgAb, which are negative for Tg by immunoassay, tested positive by LC-MS/MS. Therefore, measuring of Tg by mass spectrometry is the preferred method in TgAb positive patients. The decision levels listed below, are for thyroid cancer follow up of athyrotic patients and apply to unstimulated and stimulated thyroglobulin measurements. Decision levels are based on best practice guidelines and the literature, which includes Mayo Clinic studies. Decision levels for thyroid cancer patients, who are not completely athyrotic (ie, patient has some remnant normal thyroid tissue), have not been established, but are likely to be somewhat higher: remnant normal thyroid tissue contributes to serum Tg concentrations 0.5 to 1.0 ng/mL per gram of remnant tissue, depending on the thyroid-stimulating hormone (TSH) level. Tg <0.1 ng/mL: Tg levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels <0.1 ng/mL in athyrotic individuals on suppressive therapy indicate a minimal risk (<1-2%) of clinically detectable recurrent papillary/follicular thyroid cancer. Tg > or =0.1 to 2.0 ng/mL: Tg levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels 0.1 to 2.0 ng/mL in athyrotic individuals on suppressive therapy indicate a low risk of clinically detectable recurrent papillary/follicular thyroid cancer. Tg 2.1 to 9.9 ng/mL: Tg levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels 2.1 to 9.9 ng/mL in athyrotic individuals on suppressive therapy indicate an increased risk of clinically detectable recurrent...
papillary/follicular thyroid cancer. Tg > or =10 ng/mL: Tg levels must be interpreted in the context of TSH levels, serial Tg measurements and radioiodine ablation status. Tg levels > or =10 ng/mL in athyrotic individuals on suppressive therapy indicate a significant risk (>25%) of clinically detectable recurrent papillary/follicular thyroid cancer.

**Reference Values:**

**THYROGLOBULIN, TUMOR MARKER**

- Athyrotic: <0.1 ng/mL
- Intact thyroid < or =33 ng/mL

**THYROGLOBULIN ANTIBODY**

- < 4.0 IU/mL

Reference values apply to all ages.

**Clinical References:**


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**Thyroid Autoantibodies Profile, Serum**

**Clinical Information:** See individual unit codes.

**Useful For:** See individual unit codes.

**Interpretation:** See individual unit codes.

**Reference Values:**

**THYROGLOBULIN ANTIBODY**

- <4.0 IU/mL

Reference values apply to all ages.

**THYROPEROXIDASE ANTIBODIES**

- <9.0 IU/mL

Reference values apply to all ages.

**Clinical References:** See individual unit codes.

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**Thyroid Function Cascade, Serum**

**Clinical Information:** This test utilizes a cascaded testing procedure to efficiently evaluate and monitor functional thyroid status. The cascade begins with thyroid-stimulating hormone (TSH) as a screening assay. In patients with an intact pituitary-thyroid axis, TSH provides a physiologic indicator of the functional level of thyroid hormone activity. Increased TSH indicates inadequate thyroid hormone, and suppressed TSH indicates excess thyroid hormone. Transient TSH abnormalities may be found in seriously ill, hospitalized patients, so this is not the ideal setting to assess thyroid function. However, even in these patients, TSH works better than total thyroxine (an alternative screening test). When TSH is normal, no additional testing will be necessary. However, when the TSH result is abnormal, appropriate follow-up tests will automatically be performed. If TSH is below 0.3 mIU/L or above 4.2 mIU/L, free thyroxine (FT4) is performed. The supplemental measurement of FT4 in patients with abnormal TSH measurements allows one to better assess the severity of the changes. Serum
triiodothyronine (T3) levels often are depressed in sick and hospitalized patients, caused in part by the biochemical shift to the production of reverse T3. Therefore, T3 generally is not a reliable predictor of hypothyroidism. However, in a small subset of hyperthyroid patients, hyperthyroidism may be caused by overproduction of T3 (T3 toxicosis). To help diagnose and monitor this subgroup, T3 is measured on all specimens with suppressed TSH and normal FT4 concentrations. Detectable concentrations of antithyroperoxidase (anti-TPO) antibodies are observed in patients with autoimmune thyroiditis and may cause the destruction of thyroid tissue, eventually resulting in hypothyroidism. Anti-TPO antibodies are measured in all specimens with elevated TSH concentrations. See Thyroid Function Ordering Algorithm in Special Instructions.

**Useful For:** Screening for a diagnosis of thyroid disease

**Interpretation:** In primary hypothyroidism, thyroid-stimulating hormone (TSH) levels will be elevated. In primary hyperthyroidism, TSH levels will be low. The ability to quantitate circulating levels of TSH is important in evaluating thyroid function. It is especially useful in the differential diagnosis of primary (thyroid) from secondary (pituitary) and tertiary (hypothalamus) hypothyroidism. In primary hypothyroidism, TSH levels are significantly elevated, while in secondary and tertiary hypothyroidism, TSH levels are low or normal. Elevated or low TSH in the context of normal free thyroxine is often referred to as subclinical hypo- or hyperthyroidism, respectively. Thyrotropin-releasing hormone (TRH) stimulation differentiates all types of hypothyroidism by observing the change in patient TSH levels in response to TRH. Typically, the TSH response to TRH stimulation is exaggerated in cases of primary hypothyroidism, absent in secondary hypothyroidism, and delayed in tertiary hypothyroidism. Most individuals with primary hyperthyroidism have TSH suppression and do not respond to TRH stimulation test with an increase in TSH over their basal value. Sick, hospitalized patients may have falsely low or transiently elevated TSH.

**Reference Values:**
- 0-5 days: 0.7-15.2 mIU/L
- 6 days-2 months: 0.7-11.0 mIU/L
- 3-11 months: 0.7-8.4 mIU/L
- 1-5 years: 0.7-6.0 mIU/L
- 6-10 years: 0.6-4.8 mIU/L
- 11-19 years: 0.5-4.3 mIU/L
- >20 years: 0.3-4.2 mIU/L

**Clinical References:**

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Thyroid Transcription Factor (8G7G3/1) Immunostain, Technical Component Only

**Clinical Information:** Thyroid transcription factor 1 (TTF1) is a nuclear protein expressed in thyroid follicular cells, type II pneumocytes, and a subset of bronchial cells. Given its relative specificity for cells of thyroid or lung origin, this immunostain is often included in a panel to identify the primary site for carcinomas of unknown origin.

**Useful For:** Identification of thyroid or lung cells as the primary tumor site in carcinomas of unknown origin

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation.
for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**TTFSP**

**Thyroid Transcription Factor (SPT24) Immunostain, Technical Component Only**

**Clinical Information:** Thyroid transcription factor 1 (TTF1) is a nuclear protein expressed in thyroid follicular cells, type II pneumocytes, and a subset of bronchial cells. Given its relative specificity for cells of thyroid or lung origin, this immunostain is often included in a panel to identify the primary site for carcinomas of unknown origin.

**Useful For:** Part of a panel of immunostains to identify the primary site for carcinomas of unknown origin

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**TTFK5**

**Thyroid Transcription Factor 1 (TTF1) (SPT24) + Keratin 5/6 (KRT5/6) Immunostain, Technical Component**

**Clinical Information:** Thyroid transcription factor 1 (TTF1) is a nuclear protein (detected by the chromogen 3,3'-diaminobenzidine: DAB) expressed in thyroid follicular cells, type II pneumocytes, and a subset of bronchial cells. Keratin 5/6 is a cocktail of high-molecular-weight keratins. Squamous
epithelium of normal skin stains in a cytoplasmic pattern with keratin 5/6 (detected by the chromogen fast red). Keratin 5/6 is usually positive in mesotheliomas and negative in adenocarcinomas, making it useful in separating mesotheliomas from pulmonary adenocarcinomas. This immunostain is often included in a panel to identify the primary site for carcinomas of unknown origin.

**Useful For:** Thyroid transcription factor 1 aids in the classification of carcinomas of unknown origin
Keratin 5/6 aids in the identification of cells expressing high-molecular-weight cytokeratin

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

### TSH

**Thyroid-Stimulating Hormone (TSH), Beta Immunostain, Technical Component Only**

**Clinical Information:** Thyroid-stimulating hormone (TSH) stimulates thyroid growth and production of thyroid hormones. TSH-producing cells constitute approximately 5% of the cells of the normal anterior pituitary. Antibodies to TSH are used in a panel to subclassify pituitary adenomas.

**Useful For:** Part of a panel of immunostains used in the classification of pituitary adenomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

### STSH

**Thyroid-Stimulating Hormone-Sensitive (s-TSH), Serum**

**Clinical Information:** Thyroid-stimulating hormone (TSH, thyrotropin) is a glycoprotein hormone consisting of 2 subunits. The alpha subunit is similar to those of follicle-stimulating hormone, human
chorionic gonadotropin, and luteinizing hormone. The beta subunit is different from those of the other
glycoprotein hormones and confers its biochemical specificity. TSH is synthesized and secreted by the
anterior pituitary in response to a negative feedback mechanism involving concentrations of free
triiodothyronine and free thyroxine. Additionally, the hypothalamic tripeptide, thyrotropin-releasing
hormone, directly stimulates TSH production. TSH interacts with specific cell receptors on the thyroid
cell surface and gives rise to 2 main actions. First, it stimulates cell reproduction and hypertrophy.
Second, it stimulates the thyroid gland to synthesize and secrete triiodothyronine and thyroxine. Serum
TSH concentrations exhibit a diurnal variation with the peak occurring during the night and the nadir
occurring between 10 a.m. and 4 p.m. This biological variation does not influence the interpretation of the
test result since most clinical TSH measurements are performed on ambulatory patients between 8 a.m.
and 6 p.m. When hypothalamic-pituitary function is normal, a log/linear inverse relationship between
serum TSH and free thyroxine exists. See Thyroid Function Ordering Algorithm in Special Instructions.

**Useful For:** Screening for thyroid dysfunction and detecting mild (subclinical), as well as overt,
primary hyp- or hyperthyroidism in ambulatory patients Monitoring patients on thyroid replacement
therapy Confirmation of thyroid-stimulating hormone (TSH) suppression in thyroid cancer patients on
thyroxine suppression therapy Prediction of thyrotropin-releasing hormone-stimulated TSH response

**Interpretation:** In primary hypothyroidism, thyroid-stimulating hormone (TSH) levels will be
elevated. In primary hyperthyroidism, TSH levels will be low. The ability to quantitate circulating
levels of TSH is important in evaluating thyroid function. It is especially useful in the differential
diagnosis of primary (thyroid) from secondary (pituitary) and tertiary (hypothalamus) hypothyroidism.
In primary hypothyroidism, TSH levels are significantly elevated, while in secondary and tertiary
hypothyroidism, TSH levels are low or normal. Elevated or low TSH in the context of normal free
thyroxine is often referred to as subclinical hypo- or hyperthyroidism, respectively.
Thyrotropin-releasing hormone (TRH) stimulation differentiates all types of hypothyroidism by
observing the change in patient TSH levels in response to TRH. Typically, the TSH response to TRH
stimulation is exaggerated in cases of primary hypothyroidism, absent in secondary hypothyroidism,
and delayed in tertiary hypothyroidism. Most individuals with primary hyperthyroidism have TSH
suppression and do not respond to TRH stimulation with an increase in TSH over their basal value.
Sick, hospitalized patients may have falsely low or transiently elevated TSH.

**Reference Values:**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Reference Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 days</td>
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<tr>
<td>3-11 months</td>
<td>0.7-8.4 mIU/L</td>
</tr>
<tr>
<td>1-5 years</td>
<td>0.7-6.0 mIU/L</td>
</tr>
<tr>
<td>6-10 years</td>
<td>0.6-4.8 mIU/L</td>
</tr>
<tr>
<td>11-19 years</td>
<td>0.5-4.3 mIU/L</td>
</tr>
<tr>
<td>&gt; or =20 years</td>
<td>0.3-4.2 mIU/L</td>
</tr>
</tbody>
</table>

For SI unit Reference Values, see

**Clinical References:**
decisions to initiate thyroxine therapy for patients with mildly increased serum thyrotropin (5.1-10.0
Ninth edition, Roche Diagnostics Ltd, Rotkreuz, Switzerland July 2009, V9.1

**Thyroid-Stimulating Immunoglobulin (TSI), Serum**

**Clinical Information:** Autoimmune thyroid disease is characterized by the presence of
autoantibodies against various thyroid components, namely the thyrotropin receptor (thyroid-stimulating
hormone receptor: TSHR), thyroid-peroxidase (TPO), and thyroglobulin (Tg), as well as an
inflammatory cellular infiltrate of variable intensity within the gland. Among the autoantibodies found in
autoimmune thyroid disease, TSHR autoantibodies are most closely associated with disease pathogenesis. All forms of autoimmune thyrotoxicosis (Graves disease, Hashitoxicosis, neonatal thyrotoxicosis) are caused by the production of TSHR-stimulating autoantibodies. The role of the TPO and Tg autoantibodies in either autoimmune thyrotoxicosis or autoimmune hypothyroidism is less well established; they may merely represent epiphenomena. Detectable concentrations of anti-TPO antibodies are observed in most patients with autoimmune thyroid disease (eg, Hashimoto thyroiditis, idiopathic myxedema, and Graves disease). Autoantibodies that bind and transactivate the TSHR lead to stimulation of the thyroid gland independent of the normal feedback-regulated thyroid-stimulating hormone (TSH) stimulation. These TSHR autoantibodies also are known as long-acting-thyroid-stimulator or thyroid-stimulating immunoglobulins (TSI). Some patients with Graves disease also have TSHR-blocking antibodies, which do not transactivate the TSHR. The balance between TSI and TSHR-blocking antibodies, as well as their individual titers, are felt to be determinants of Graves disease severity. At least 20% of patients with autoimmune hypothyroidism also have evidence either of TSHR-blocking antibodies or, less commonly, TSI. TSHR autoantibodies may be found before autoimmune thyrotoxicosis becomes biochemically or clinically manifest. Since none of the treatments for Graves disease are aimed at the underlying disease process, but rather ablate thyroid tissue or block thyroid hormone synthesis, TSI may persist after apparent cure. TSI are IgG antibodies and can, therefore, cross the placental barrier, causing neonatal thyrotoxicosis. First-order tests for autoimmune thyroid disease include TPO / Thyroperoxidase (TPO) Antibodies, Serum (most suited for suspected cases of autoimmune hypothyroidism) and THYRO / Thyrotropin Receptor Antibody, Serum. Thyrotropin receptor antibody (TSHR-antibody) is a binding assay that detects both TSI and TSHR-blocking autoantibodies; it can be used instead of this TSI assay for most applications, as long as the results are interpreted in the clinical context. The TSHR-antibody test has a shorter turnaround time than the TSI assay, is less expensive, and if interpreted within the clinical context, has excellent correlation with the TSI assay. Specific detection of TSI is accomplished by this second-order bioassay.

Useful For: Second-order testing for autoimmune thyroid disease, including: -Differential diagnosis of etiology of thyrotoxicosis in patients with ambiguous clinical signs or contraindicated (eg, pregnant or breast-feeding) or indeterminate thyroid radioisotope scans -Diagnosis of clinically suspected Graves disease (eg, extrathyroidal manifestations of Graves disease: endocrine exophthalmos, pretibial myxedema, thyroid acropathy) but normal thyroid function tests -Determining the risk of neonatal thyrotoxicosis in a fetus of a pregnant female with active or past Graves disease -Differential diagnosis of gestational thyrotoxicosis versus first-trimester manifestation or recurrence of Graves disease -Assessing the risk of Graves disease relapse after antithyroid drug treatment A combination of TSI / Thyroid-Stimulating Immunoglobulin (TSI), Serum and THYRO / Thyrotropin Receptor Antibody, Serum is useful as an adjunct in the diagnosis of unusual cases of hypothyroidism (eg, Hashitoxicosis).

Interpretation: The sensitivity and specificity of an elevated thyroid-stimulating immunoglobulins (TSI) index for Graves disease diagnosis depends on whether patients have clinically active, untreated disease or disease treated with antithyroid drugs. Using a TSI index of 1.3 as the cutoff level in newly diagnosed, untreated patients, the sensitivity and specificity are higher than 90%. For a higher cutoff of 1.8, specificity approaches 100%, but sensitivity decreases somewhat. In patients with inactive or treated Graves disease the specificity is similar, while sensitivity is lower, ranging from 50% to 80%. Significant neonatal thyrotoxicosis is likely if a pregnant woman with a history of Graves disease has a TSI index above 3.9 during the last trimester, regardless of her remission status. Lesser elevations are only occasionally associated with neonatal thyrotoxicosis. This is particularly relevant for women who have previously undergone thyroid-ablative therapy or are on active antithyroid drug treatment and, therefore, no longer display biochemical or clinical evidence of thyrotoxicosis. Gestational thyrotoxicosis, which is believed to be due to a combination of human chorionic gonadotropin cross-reactivity on the thyroid-stimulating hormone receptor (TSHR) and transient changes in thyroid hormone protein binding, is not associated with an elevated TSI index. Finding an elevated TSI index in this setting suggests underlying Graves disease. An elevated TSI index at the conclusion of a course of anti-thyroid drug treatment is highly predictive of relapse of Graves disease. However, the converse, a normal TSI index, is not predictive of prolonged remission. In patients with thyroid function tests that fluctuate between hypo- and hyperthyroidism or vice versa, a clearly elevated TSHR-antibody level (>25%) and a simultaneous TSI index that is normal or only minimally elevated (1.3-1.8) suggest a diagnosis of possible Hashitoxicosis.

Reference Values:

Thyroperoxidase (TPO) Antibodies, Serum

Clinical Information: Thyroperoxidase (TPO) is an enzyme involved in thyroid hormone synthesis, catalyzing the oxidation of iodide on tyrosine residues in thyroglobulin for the synthesis of triiodothyronine and thyroxine (tetraiodothyronine). TPO is a membrane-associated hemoglycoprotein expressed only in thyrocytes and is one of the most important thyroid gland antigens. Disorders of the thyroid gland are frequently caused by autoimmune mechanisms with the production of autoantibodies. Anti-TPO antibodies activate complement and are thought to be significantly involved in thyroid dysfunction and the pathogenesis of hypothyroidism. The determination of TPO antibody levels is the most sensitive test for detecting autoimmune thyroid disease (eg, Hashimoto thyroiditis, idiopathic myxedema, and Graves disease) and detectable concentrations of anti-TPO antibodies are observed in most patients with these disorders. The highest TPO antibody levels are observed in patients suffering from Hashimoto thyroiditis. In this disease, the prevalence of TPO antibodies is about 90% of cases, confirming the autoimmune origin of the disease. These autoantibodies also frequently occur (60%-80%) in the course of Graves disease. In patients with subclinical hypothyroidism, the presence of TPO antibodies is associated with an increased risk of developing overt hypothyroidism. Many clinical endocrinologists use the TPO antibody test as a diagnostic tool in deciding whether to treat a patient with subclinical hypothyroidism, and Mayo Medical Laboratories endorses this practice. See Thyroid Function Ordering Algorithm in Special Instructions.

Useful For: Aiding in the diagnosis of thyroid autoimmune disorders Differentiating thyroid autoimmune disorders from nonautoimmune goiter or hypothyroidism As a diagnostic tool in deciding whether to treat a patient who has subclinical hypothyroidism

Interpretation: Values above 9.0 IU/mL generally are associated with autoimmune thyroiditis, but elevations are also seen in other autoimmune diseases. In patients with subclinical hypothyroidism, the presence of thyroperoxidase (TPO) antibodies predicts a higher risk of developing overt hypothyroidism, 4.3% per year versus 2.1% per year in antibody-negative individuals. Furthermore, it raises the concern that such patients may be at increased risk of developing other autoimmune diseases, such as adrenal insufficiency and type 1 diabetes. The frequency of detectable anti-TPO observed in nonimmune thyroid disease is similar to the 10% to 12% observed in a healthy population with normal thyroid function. There is a good association between the presence of autoantibodies against TPO and histological thyroiditis. However, in view of the extensive regenerative capacity of the thyroid under the influence of thyroid-stimulating hormone, chronic thyroid disease may be present for years before the clinical manifestation of hypothyroidism becomes evident, if ever.

Reference Values: <9.0 IU/mL Reference values apply to all ages.

Thyro

Thyrotropin Receptor Antibody, Serum

Clinical Information: Autoimmune thyroid disease is characterized by the presence of autoantibodies against various thyroid components, namely the thyrotropin receptor (TSHR), thyroid peroxidase (TPO), and thyroglobulin (Tg), as well as by an inflammatory cellular infiltrate of variable severity within the gland. Among the autoantibodies found in autoimmune thyroid disease, TSHR autoantibodies are most closely associated with disease pathogenesis. All forms of autoimmune thyrotoxicosis (Graves disease, Hashitoxicosis, neonatal thyrotoxicosis) are caused by the production of TSHR-stimulating autoantibodies. These autoantibodies, also known as long-acting-thyroid-stimulator (LATS) or thyroid-stimulating immunoglobulins (TSI), bind to the receptor and transactivate it, leading to stimulation of the thyroid gland independent of the normal feedback-regulated thyrotropin (TSH) stimulation. Some patients with Graves disease also have TSHR-blocking antibodies, which do not transactivate the TSHR. The balance between TSI and TSHR-blocking antibodies, as well as their individual titers, are felt to be determinants of Graves disease severity. Some patients with autoimmune hypothyroidism also have evidence of either TSHR-blocking antibodies or, rarely, TSI. TSHR autoantibodies may be detected before autoimmune thyrotoxicosis becomes biochemically or clinically manifest. Since none of the treatments for Graves disease are aimed at the underlying disease process, but rather ablate thyroid tissue or block thyroid hormone synthesis, TSI may persist after apparent clinical cure. This is of particular relevance for pregnant women with a history of Graves disease that was treated with thyroid-ablative therapy. Some of these women may continue to produce TSI. Since TSI are IgG antibodies, they can cross the placental barrier causing neonatal thyrotoxicosis. While the gold standard for thyroid-stimulating immunoglobulins is the bioassay (see TSI / Thyroid-Stimulating Immunoglobulin [TSI], Serum), the thyrotropin receptor antibody test has a shorter turnaround time, less analytical variability, and is less expensive.

Useful For: Recommended first-line test for detection of thyrotropin receptor (TSHR) antibodies, and used in the following situations: - Differential diagnosis of etiology of thyrotoxicosis in patients with ambiguous clinical findings and/or contraindicated (e.g., pregnant or breast-feeding) or nondiagnostic thyroid radioisotope scans - Diagnosis of clinically suspected Graves disease (e.g., extrathyroidal manifestation of Graves disease include endocrine exophthalmos, pretibial myxedema, thyroid acropachy) in patients with normal thyroid function tests - Determining the risk of neonatal thyrotoxicosis in a fetus of a pregnant female with active or past active Graves disease - Differential diagnosis of gestational thyrotoxicosis versus first trimester manifestation or recurrence of Graves disease - Assessing the risk of Graves disease relapse after antithyroid drug treatment

Interpretation: The sensitivity and specificity of an elevated thyrotropin receptor antibody (TRAb) test for Graves disease diagnosis depends on whether patients have disease treated with antithyroid drugs or clinically active, untreated disease. Based on a study that included specimens from 436 apparently healthy individuals, 210 patients with thyroid diseases without diagnosis of Graves disease, and 102 patients with untreated Graves disease, a decision limit of 1.75 IU/L showed a sensitivity of 97% and a specificity of 99% for detection of Graves disease. In healthy individuals and in patients with thyroid disease without diagnosis of Graves disease, the upper limit of antithyrotropin receptor (anti-TSHR) values are 1.22 IU/L and 1.58 IU/L, respectively (97.5th percentiles). A Mayo study of 115 patients, including 42 patients with Graves disease, showed a sensitivity of 95% and a specificity of 97% for detection of Graves disease at a decision limit of 1.75 IU/L. Assessment of TRAb status is particularly relevant in women who have undergone thyroid ablative therapy or are on active antithyroid treatment and, therefore, no longer display biochemical or clinical evidence of thyrotoxicosis. Significant neonatal thyrotoxicosis is likely if a pregnant woman with a history of Graves disease has TRAb concentrations of >3.25 IU/L during the last trimester, regardless of her clinical remission status. Lesser elevations are only occasionally associated with neonatal thyrotoxicosis. Gestational thyrotoxicosis, which is believed to be due to a combination of human chorionic gonadotropin cross-reactivity on the TSHR and transient changes in thyroid hormone protein binding, is only very rarely associated with an elevated TRAb test. Finding an elevated TRAb test in this setting suggests usually underlying Graves disease. An elevated TRAb test at the conclusion of a course of antithyroid drug treatment is highly predictive of relapse of Graves disease. However, the converse, a normal TRAb test, is not predictive of prolonged remission.

Reference Values:
< or =1.75 IU/L
**Thyroxine-Binding Globulin (TBG), Serum**

**Clinical Information:** Thyroxine binding globulin (TBG) is the high-affinity serum binding protein for thyroxine and triiodothyronine. Normally, the thyroid adjusts to changing concentrations of TBG by producing more or less thyroid hormone to maintain a constant level of metabolically important free hormone. Elevated TBG levels are associated with influences such as pregnancy, genetic predisposition, oral contraceptives, and estrogen therapy. TBG levels can decrease with androgenic or anabolic steroids, large doses of glucocorticoids, hypoproteinemic states, liver disease, nephrotic syndrome, and congenital TBG variants.

**Useful For:** Determination of thyroxine-binding globulin levels is particularly useful for cases in which total thyroid hormone levels do not correlate with the thyrometabolic status, most commonly with pregnancy or the use of contraceptive steroids.

**Interpretation:** A change in thyroxine-binding globulin (TBG) concentration may be of hereditary, pathophysiologic, or pharmacologic origin. The TBG concentration indicates whether an abnormally high or low total thyroid hormone concentration is offset by a parallel increase or decrease in TBG concentration. In TBG deficiency, one may find euthyroid patients with extremely low total thyroxine (T4) values. Conversely, patients with high TBG levels may be clinically euthyroid with high serum total T4 values. Twenty-four specimens obtained during various stages of pregnancy yielded results ranging from 27 to 66 mcg/mL with a median of 43 mcg/mL. The literature suggests 47 to 59 mcg/mL as the range of TBG values expected during the third trimester of pregnancy.

**Reference Values:**
- Males: 12-26 mcg/mL
- Females: 11-27 mcg/mL

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.

**Clinical References:**

**Thyroxine-Binding Protein Electrophoresis, Serum**

**Clinical Information:** Normally, almost all thyroxine (99.5%) is bound to thyroxine-binding globulin, prealbumin, and albumin. Deficiencies and aberrant forms of these binding proteins can occur, causing difficulties interpreting thyroid function test results. Such abnormalities may be identified by thyroxine-binding protein electrophoresis.

**Useful For:** Explaining unusual thyroxine (T4), free T4, and thyroxine-binding globulin (TBG) test results that do not correlate with the patient’s clinical presentation. Detecting the presence of aberrant thyroxine-binding proteins such as abnormal forms of albumin and prealbumin. Detecting selective deficiency of one of the thyroxine-binding proteins. Detecting antibodies to T4. An adjunct to the diagnosis of patients with high T4 concentration due to peripheral hormone resistance by ruling out thyroxine-binding abnormalities.

**Interpretation:** Rare protein-binding abnormalities may be suspected in euthyroid patients having an
elevated total thyroxine (T4) but normal thyroxine-binding globulin (TBG). The following example is from a healthy 40-year-old male with familial dysalbuminemic hyperthyroxinemia, a benign familial condition that can be confused with hyperthyroidism: - Increased T4 of 14.4 mcg/dL (normal=5.0-12.5 mcg/dL) - Normal TBG of 20.1 mcg/dL (normal=12-26 mcg/mL) The thyroxine-binding protein electrophoresis (TBPE) assay identified that of the saturating dose of (125)I-T4: -52% was bound to albumin (normal 12%-34%) -36% was bound to thyroxine-binding prealbumin (normal 49%-70%) -13% was bound to TBG (normal 10%-25%) In this example, based on the TBPE findings, this patient’s increased serum T4 was due to increased binding to albumin. This was suggestive of familial dysalbuminemic hyperthyroxinemia (FDH), an inherited abnormality characterized by the presence of a variant serum albumin with preferential affinity for T4.

Reference Values:
THYROXINE-BINDING PROTEIN ELECTROPHORESIS
  10.3-24.9 mcg T4/dL bound to TBG
  11.5-34.1 mcg T4/dL bound to albumin
  48.8-70.4 mcg T4/dL bound to prealbumin

T4 (THYROXINE), TOTAL ONLY
  Adult (> or =20 years): 4.5-11.7 mcg/dL
  Pediatric:
  0-5 days: 5.0-18.5 mcg/dL
  6 days-2 months: 5.4-17.0 mcg/dL
  3-11 months: 5.7-16.0 mcg/dL
  1-5 years: 6.0-14.7 mcg/dL
  6-10 years: 6.0-13.8 mcg/dL
  11-19 years: 5.9-13.2 mcg/dL


FGTIA
75019

Tiagabine (Gabitril), Serum

Reference Values:
Report Limit: 5.0 ng/mL
Reference Range: <235.0 ng/mL

Therapeutic and toxic ranges have not been established.

Peak concentrations are expected at 45 minutes post dose; steady state is generally attained within 2 days.

Observed tiagabine concentrations in clinical trials (30 â€“ 56 mg/day): <1 â€“ 234 ng/mL.

Measured tiagabine concentrations, post marketing (95% confidence interval): 0 â€“ 440 ng/mL.

Note: The 95% confidence interval for tiagabine concentrations determined by MEDTOX Laboratories will be updated periodically as more information becomes available.

TICKS
83265

Tick-Borne Disease Antibodies Panel, Serum

Clinical Information: In North America, ticks are the primary vectors of infectious diseases.(1) Worldwide, ticks rank second only to mosquitoes in disease transmission. In the United States, tick-borne diseases include Lyme disease, Rocky Mountain spotted fever, human monocytic and granulocytic ehrlichiosis, babesiosis, tularemia, relapsing fever, and Colorado tick fever. Symptoms of the various
tick-vector ed diseases range from mild to life-threatening. Early symptoms, which include fever, aches, and malaise, do not aid in distinguishing the various diseases. Because early treatment can minimize or eliminate the risk of severe disease, early detection is essential, yet patients may not have developed distinctive symptoms to help in the differential diagnosis. A tick-borne panel can assist in identifying the pathogen, allowing treatment to be initiated. For information on the specific diseases, please see the individual unit codes.

**Useful For:** Evaluation of the most common tick-borne diseases found in the United States, including Lyme disease, human monocytic and granulocytic ehrlichiosis, and babesiosis Evaluation of patients with a history of, or suspected, tick exposure who are presenting with fever, myalgia, headache, nausea, and other nonspecific symptoms

**Interpretation:**
- **Ehrlichia chaffeensis:** A positive immunofluorescence assay (titer $\geq 1:64$) suggests current or previous infection with Ehrlichia chaffeensis. In general, the higher the titer, the more likely the patient has an active infection. Four-fold rises in titer also indicate active infection.
- **Anaplasma phagocytophilum:** A positive result of an immunofluorescence assay (IFA) test (titer $> 1:64$) suggests current or previous infection with human granulocytic ehrlichiosis. In general, the higher the titer, the more likely it is that the patient has an active infection. Seroconversion may also be demonstrated by a significant increase in IFA titers. During the acute phase of the infection, serologic tests are often nonreactive, PCR testing is available to aid in the diagnosis of these cases (see EHRL / Ehrlichia/Anaplasma, Molecular Detection, PCR, Blood).
- **Babesia microti:** A positive result of an indirect fluorescent antibody test (titer $> 1:64$) suggests current or previous infection with Babesia microti. In general, the higher the titer, the more likely it is that the patient has an active infection. Patients with documented infections have usually had titers ranging from 1:320 to 1:2,560. Lyme Disease: Negative: No evidence of antibodies to Borrelia burgdorferi detected. False-negative results may occur in recently infected patients ($< 2$ weeks) due to low or undetectable antibody levels to B burgdorferi. If recent exposure is suspected, a second sample should be collected and tested in 2 to 4 weeks. Equivocal: Not diagnostic. Supplemental testing by immunoblot has been ordered by reflex. Positive: Not diagnostic. Supplemental testing by immunoblot has been ordered by reflex.

**Reference Values:**
- **Ehrlichia chaffeensis (HME) ANTIBODY, IgG**
  - $< 1:64$
  - Reference values apply to all ages.

- **Anaplasma phagocytophilum ANTIBODY, IgG**
  - $< 1:64$
  - Reference values apply to all ages.

- **Babesia microti IgG ANTIBODIES**
  - $< 1:64$
  - Reference values apply to all ages.

- **LYME DISEASE SEROLOGY**
  - **Negative**
  - Reference values apply to all ages.

**Clinical References:** Mathieu ME, Wilson BB: Ticks (including tick paralysis). In Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, Vol 1. Fifth edition. Edited by GL Mandell, JE Bennett, R Dolin. Philadelphia, Churchill Livingston, 2000, pp 2980-2983

**Clinical Information:** Ticks are the primary vectors of infectious diseases in North America, and rank second only to mosquitoes in disease transmission worldwide. In the United States, tick-borne diseases include Lyme disease, Rocky Mountain spotted fever, human monocytic ehrlichiosis, human granulocytic anaplasmosis, babesiosis, tularemia, relapsing fever, Colorado tick fever, and Borrelia miyamotoi infection. (1) Several of these diseases are transmitted by the same tick, and coinfections are
ocasionally seen. In particular, *Ixodes* species ticks are capable to transmitting the causative agents of Lyme disease (*B. burgdorferi* and *B. mayonii*), anaplasmosis (*Anaplasma phagocytophilum*), and babesiosis (*Babesia* species). These diseases are prevalent throughout the northeastern and upper Midwestern states and parts of the Pacific Northwest. Symptoms of the various tick-vectored diseases range from mild to life-threatening. Early symptoms, which include fever, aches, and malaise, do not aid in distinguishing the various diseases. Because early treatment can minimize or eliminate the risk of severe disease, early detection is essential, yet patients may not have developed distinctive symptoms to help in the differential diagnosis. A rapid tick-borne PCR panel can assist in identifying the pathogen, allowing treatment to be initiated. While Lyme disease due to *B. burgdorferi* is best detected through 2-tiered serologic testing, acute ehrlichiosis, anaplasmosis, babesiosis, and *B. miyamotoi* infection are best detected using molecular amplification assays. This tick-borne panel offers sensitive, specific, and rapid detection of the agents that cause these 4 diseases. For information on the specific diseases, see the individual test IDs.

**Useful For:** Evaluation of patients with suspected human monocytic ehrlichiosis, human granulocytic anaplasmosis, babesiosis, or *Borrelia miyamotoi* infection. Evaluation of patients with a history of, or suspected, tick exposure who are presenting with fever, myalgia, headache, nausea, and other nonspecific symptoms.

**Interpretation:**
*Borrelia miyamotoi:* A positive result indicates the presence of *B. miyamotoi* DNA and is consistent with active or recent infection. While positive results are highly specific indicators of disease, they should be correlated with symptoms and clinical findings of tick-borne relapsing fever.
*Ehrlichia/Anaplasma:* Positive results indicate presence of specific DNA from *Ehrlichia chaffeensis*, *E. ewingii*, *E. muris*-like organism, or *A. phagocytophilum* and support the diagnosis of ehrlichiosis or anaplasmosis. Negative results indicate absence of detectable DNA from any of these 4 pathogens in specimens, but it does not exclude the presence of the organism or active or recent disease. Since DNA of *E. ewingii* is indistinguishable from that of *E. canis* by this rapid PCR assay, a positive result for *E. ewingii/canis* indicates the presence of DNA from either of these 2 organisms.
*Babesia:* A positive result indicates the presence of *Babesia* species DNA and is consistent with active or recent infection. While positive results are highly specific indicators of disease, they should be correlated with blood smear microscopy, serological results and clinical findings. A negative result indicates absence of detectable DNA from *Babesia* species in the specimen, but does not always rule-out ongoing babesiosis in a seropositive person, since the parasitemia may be present at a very low level or may be sporadic. Other tests to consider in the evaluation of a patient presenting with an acute febrile illness following tick exposure include serologic tests for Lyme disease (*B. burgdorferi*), and molecular detection (PCR) for ehrlichiosis/anaplasmosis. For patients who are past the acute stage of infection, serologic tests for these organisms should be ordered prior to PCR testing.

**Reference Values:**
*Babesia* species, MOLECULAR DETECTION, PCR
Negative

*Ehrlichia/Anaplasma,* MOLECULAR DETECTION, PCR
Negative

*Borrelia miyamotoi,* MOLECULAR DETECTION, PCR
Negative


**FFTIC**

**Ticlopidine, Serum/Plasma**

**Reference Values:** Reporting limit determined each analysis

Ticlopidine
Synonym(s): Ticlid
Steady state peak plasma levels from patients on a 250 mg twice daily regimen: 0.22–2.1 mcg/mL (mean of 0.99) at 2 hours post dose.

**Tilapia IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal 1 0.35-0.69 Low Positive 2 0.70-3.4 Moderate Positive 3 3.5-17.4 High Positive 4 17.5-49.9 Very High Positive 5 50.0-99.9 Very High Positive 6 >100 Very High Positive

**Reference Values:**

<0.35 kU/L

**Timothy Grass, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69 Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49 Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4 Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9 Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9 Strongly positive</td>
</tr>
<tr>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

Tin, Blood

Reference Values:
Reference Range: <5.0 ng/mL

Toxic range not established.

Tin, Serum

Reference Values:
Reference Range: <5.0 ng/mL

Toxic range has not been established.

Note: Whole blood is the preferred specimen for monitoring exposure to tin.

Tissue Drug Screen

Reference Values:
Testing is complete. Report has been attached in Mayo Access.

Tissue Transglutaminase (tTG) Antibodies, IgA and IgG Profile, Serum

Clinical Information: Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process following ingestion of wheat, rye, or barley proteins that occurs in genetically susceptible individuals. The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and constipation. Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma. The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency. Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population. A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy. Given the invasive nature and cost of the biopsy, serologic and genetic laboratory tests may be used to identify individuals with a high probability of having celiac disease. Subsequently, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures (see Celiac Disease Diagnostic Testing Algorithm in Special Instructions. In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies. Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves. This is typically accompanied by an improvement in clinical symptoms. For your convenience, we recommend utilizing cascade testing for celiac disease. Cascade testing ensures...
that testing proceeds in an algorithmic fashion. The following cascades are available; select the appropriate 1 for your specific patient situation. -CDCOM / Celiac Disease Comprehensive Cascade: complete testing including HLA DQ -CDSP / Celiac Disease Serology Cascade: complete testing excluding HLA DQ -CDGF / Celiac Disease Gluten-Free Cascade: for patients already adhering to a gluten-free diet

**Useful For:** Evaluating patients suspected of having celiac disease, including patients with compatible clinical symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disease, positivity for HLA DQ2 and/or DQ8) Monitoring adherence to gluten-free diet in patients with dermatitis herpetiformis and celiac disease

**Interpretation:** The finding of tissue transglutaminase (tTG) IgA antibodies is specific for celiac disease and possibly for dermatitis herpetiformis. For individuals with moderately to strongly positive results, a diagnosis of celiac disease is likely and the patient should undergo biopsy to confirm the diagnosis. The finding of tTG IgG antibodies may indicate a diagnosis of celiac disease, particularly in individuals who are IgA deficient. For individuals with moderately to strongly positive results, a diagnosis of celiac disease is possible and the patient should undergo a biopsy to confirm the diagnosis. If patients strictly adhere to a gluten-free diet, the unit value of anti-tTG antibodies should begin to decrease within 6 to 12 months of onset of dietary therapy.

**Reference Values:**
- **tTG ANTIBODY, IgA**
  - <4.0 U/mL (negative)
  - 4.0-10.0 U/mL (weak positive)
  - >10.0 U/mL (positive)
  - Reference values apply to all ages.
- **tTG ANTIBODY, IgG**
  - <6.0 U/mL (negative)
  - 6.0-9.0 U/mL (weak positive)
  - >9.0 U/mL (positive)
  - Reference values apply to all ages.

**Clinical References:**

**Tissue Transglutaminase (tTG) Antibody, IgA, Serum**

**Clinical Information:** Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process following ingestion of wheat, rye, or barley proteins that occurs in genetically susceptible individuals. The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and constipation. Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia, and dermatitis herpetiformis. Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma. The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency. Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population. A definitive diagnosis of celiac
disease requires a jejunal biopsy demonstrating villous atrophy. Given the invasive nature and cost of the biopsy, serologic and genetic laboratory tests may be used to identify individuals with a high probability of having celiac disease. Subsequently, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures (see Celiac Disease Diagnostic Testing Algorithm in Special Instructions). In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies. Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves. This is typically accompanied by an improvement in clinical symptoms. See Celiac Disease Diagnostic Testing Algorithm in Special Instructions for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions. For your convenience, we recommend utilizing cascade testing for celiac disease. Cascade testing ensures that testing proceeds in an algorithmic fashion. The following cascades are available; select the appropriate 1 for your specific patient situation. Algorithms for the cascade tests are available in Special Instructions. -CDCCOM / Celiac Disease Comprehensive Cascade: complete testing including HLA DQ -CDSP / Celiac Disease Serology Cascade: complete testing excluding HLA DQ -CDGF / Celiac Disease Gluten-Free Cascade: for patients already adhering to a gluten-free diet To order individual tests, see Celiac Disease Diagnostic Testing Algorithm in Special Instructions. -CDCOM / Celiac Disease Comprehensive Cascade: complete testing including HLA DQ -CDSP / Celiac Disease Serology Cascade: complete testing excluding HLA DQ -CDGF / Celiac Disease Gluten-Free Cascade: for patients already adhering to a gluten-free diet

**Useful For:** Evaluating patients suspected of having celiac disease, including patients with compatible clinical symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disorder, positivity for HLA DQ2 and/or DQ8) Screening test for dermatitis herpetiformis, in conjunction with endomysial antibody test Monitoring adherence to gluten-free diet in patients with dermatitis herpetiformis and celiac disease

**Interpretation:** The finding of tissue transglutaminase (tTG)-IgA antibodies is specific for celiac disease and possibly for dermatitis herpetiformis. For individuals with moderately to strongly positive results, a diagnosis of celiac disease is likely and the patient should undergo biopsy to confirm the diagnosis. If patients strictly adhere to a gluten-free diet, the unit value of IgA-anti-tTG should begin to decrease within 6 to 12 months of onset of dietary therapy.

**Reference Values:**

- <4.0 U/mL (negative)
- 4.0-10.0 U/mL (weak positive)
- >10.0 U/mL (positive)

Reference values apply to all ages.

**Clinical References:**

**TTGG**

**Tissue Transglutaminase (tTG) Antibody, IgG, Serum**

**Clinical Information:** Celiac disease (gluten-sensitive enteropathy, celiac sprue) results from an immune-mediated inflammatory process following ingestion of wheat, rye, or barley proteins that occurs in genetically susceptible individuals. The inflammation in celiac disease occurs primarily in the mucosa of the small intestine, which leads to villous atrophy. Common clinical manifestations related to gastrointestinal inflammation include abdominal pain, malabsorption, diarrhea, and constipation. Clinical symptoms of celiac disease are not restricted to the gastrointestinal tract. Other common manifestations of celiac disease include failure to grow (delayed puberty and short stature), iron deficiency, recurrent fetal loss, osteoporosis, chronic fatigue, recurrent aphthous stomatitis (canker sores), dental enamel hypoplasia,
and dermatitis herpetiformis. Patients with celiac disease may also present with neuropsychiatric manifestations including ataxia and peripheral neuropathy, and are at increased risk for development of non-Hodgkin lymphoma. The disease is also associated with other clinical disorders including thyroiditis, type I diabetes mellitus, Down syndrome, and IgA deficiency. Celiac disease tends to occur in families; individuals with family members who have celiac disease are at increased risk of developing the disease. Genetic susceptibility is related to specific HLA markers. More than 97% of individuals with celiac disease in the United States have DQ2 and/or DQ8 HLA markers, compared to approximately 40% of the general population. A definitive diagnosis of celiac disease requires a jejunal biopsy demonstrating villous atrophy. Given the invasive nature and cost of the biopsy, serologic and genetic laboratory tests may be used to identify individuals with a high probability of having celiac disease. Subsequently, those individuals with positive laboratory results should be referred for small intestinal biopsy, thereby decreasing the number of unnecessary invasive procedures (see Celiac Disease Diagnostic Testing Algorithm in Special Instructions). In terms of serology, celiac disease is associated with a variety of autoantibodies, including endomysial, tissue transglutaminase (tTG), and deamidated gliadin antibodies. Although the IgA isotype of these antibodies usually predominates in celiac disease, individuals may also produce IgG isotypes, particularly if the individual is IgA deficient. The most sensitive and specific serologic tests are tTG and deamidated gliadin antibodies. The treatment for celiac disease is maintenance of a gluten-free diet. In most patients who adhere to this diet, levels of associated autoantibodies decline and villous atrophy improves. This is typically accompanied by an improvement in clinical symptoms. See Celiac Disease Diagnostic Testing Algorithm in Special Instructions for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions. For your convenience, we recommend utilizing cascade testing for celiac disease. Cascade testing ensures that testing proceeds in an algorithmic fashion. The following cascades are available; select the appropriate 1 for your specific patient situation. -CDCOM / Celiac Disease Comprehensive Cascade: complete testing including HLA DQ -CDSP / Celiac Disease Serology Cascade: complete testing excluding HLA DQ -CDGF / Celiac Disease Gluten-Free Cascade: for patients already adhering to a gluten-free diet

**Useful For:** For individuals with IgA deficiency: -Evaluating patients suspected of having celiac disease, including patients with compatible clinical symptoms, patients with atypical symptoms, and individuals at increased risk (family history, previous diagnosis with associated disorder, positivity for HLA DQ2 and/or DQ8 -Screening test for dermatitis herpetiformis, in conjunction with endomysial antibody test -Monitoring adherence to gluten-free diet in patients with dermatitis herpetiformis and celiac disease

**Interpretation:** The finding of tissue transglutaminase (tTG) IgG antibodies may indicate a diagnosis of celiac disease, particularly in individuals who are IgA deficient. For individuals with moderately to strongly positive results, a diagnosis of celiac disease is possible and the patient should undergo a biopsy to confirm the diagnosis. If patients strictly adhere to a gluten-free diet, the unit value of tTG-IgG antibodies should begin to decrease within 6 to 12 months of onset of dietary therapy. See Celiac Disease Diagnostic Testing Algorithm in Special Instructions for the recommended approach to a patient suspected of celiac disease. An algorithm is available for monitoring the patient's response to treatment, see Celiac Disease Routine Treatment Monitoring Algorithm in Special Instructions.

**Reference Values:**
- <6.0 U/mL (negative)
- 6.0-9.0 U/mL (weak positive)
- >9.0 U/mL (positive)

Reference values apply to all ages.

**Clinical References:**
Titanium, Serum

**Clinical Information:** Titanium is the ninth most abundant element in the earth’s crust. Multiple oxidation states between 2+ and 4+ allow formation of a variety of compounds. There is no evidence that titanium is an essential element. Due in part to titanium’s oxide formation propensity, the element is considered to be nontoxic. Soils, drinking water, and air all contain trace amounts of titanium. The food processing industry uses large quantities of titanium as a food additive; processed foods contain higher levels than are found in most produce and organic food-stuffs. The average daily oral intake through food consumption is 0.1 to 1 mg/day, which accounts for more than 99% of exposure. Gastrointestinal absorption of titanium is low (approximately 3%) and the majority of ingested titanium is rapidly excreted in the urine and stool. The total body burden of titanium is usually in the range of 9 to 15 mg, a significant portion of which is contained in the lung. Titanium dust entering the respiratory tract is nonirritating and is almost completely nonfibrogenic in humans. Titanium-containing alloys are used in some artificial joints, prosthetic devices, and implants. Titanium dioxide allows osseointegration between an artificial medical implant and bone. Despite their wide use, exposure to these materials has not been linked to toxicity. In one study patients monitored up to 36 months following joint replacement with titanium-containing joints showed a statistically significant increase in detectable serum titanium within the study group. While titanium concentrations are not a measure of toxicity, they are useful in determining whether implant breakdown is occurring. Serum titanium concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Monitoring metallic prosthetic implant wear

**Interpretation:** Prosthesis wear is known to result in increased circulating concentration of metal ions. In the absence of an implant, circulating titanium is <1 ng/mL. Modest increase (1.0-3.0 ng/mL) in serum titanium concentration is evident with a prosthetic device in good condition. Serum concentrations >10 ng/mL in a patient with titanium-based implant suggest prosthesis wear. Increased serum titanium concentration in the absence of corroborating clinical information does not independently predict prosthesis wear or failure.

**Reference Values:**
0-1 ng/mL

**Clinical References:**

TLE-1 Immunostain, Technical Component Only

**Clinical Information:** Transducin-like enhancer of split proteins (TLE-1) associates with chromatin, specifically with histone H3. TLE1 is upregulated in early stages of cell differentiation and may have value in the diagnosis of synovial sarcoma, where it is positive in the majority of the cases. However, this marker is not entirely specific for synovial sarcoma, and results should be interpreted in the context of other clinicopathologic and immunophenotypic features.

**Useful For:** Aids in the identification of synovial sarcoma

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is
required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**TNF-alpha (TNF-a) Serum**

**Clinical Information:** Cytokines have emerged as molecules of importance in the regulation of many immunologic processes in the cell. The ability to accurately measure quantitative and qualitative differences in cytokine production is becoming increasingly important to the understanding of normal and pathological processes.

**Reference Values:**
<5.6 pg/mL


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**TNFRSF1A Gene, Full Gene Analysis**

**Clinical Information:** Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is a hereditary autoinflammatory disease that occurs most commonly, but not exclusively, in Northern European populations. TRAPS is characterized by recurrent febrile attacks and inflammation typically lasting 1 to 3 weeks. Accompanying clinical manifestations include abdominal pain, pleuritis, arthralgia, ocular involvement (conjunctivitis, peri orbital edema, uveitis), myalgia, and cutaneous manifestations, usually migratory erythematous rash overlaying areas of myalgia. Initial presentation most often occurs in childhood but age of onset can be variable and adult-onset cases have been described. Amyloid A (AA)-type amyloidosis is a serious long-term complication in some patients with TRAPS. TRAPS is caused by mutations in the TNFRSF1A gene, a tumor necrosis factor receptor. TRAPS is inherited in an autosomal dominant fashion with reduced penetrance. Mutations in TNFRSF1A account for approximately 32% to 50% of familial cases of TRAPS, while only 2% to 10% of sporadic cases have an identifiable mutation in this gene. Limited genotype-phenotype correlations have been described, but mutations in cysteine residues are more likely to be associated with amyloidosis. Patients with TRAPS often respond to corticosteroid treatment or anti-TNF therapy (etanercept) but are typically unresponsive to colchicine therapy.

**Useful For:** Confirmation of tumor necrosis factor receptor-associated periodic syndrome (TRAPS) for patients with clinical features

**Interpretation:** All detected alterations will be evaluated according to the American College of Medical Genetics and Genomics (AMCG) recommendations. Variants will be classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.
Reference Values:
An interpretive report will be provided.


Tobacco, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.

**Clinical Information:** Tobramycin is an antibiotic used to treat life-threatening blood infections caused by gram-negative bacilli, particularly Citrobacter freundii, Enterobacter (all species), Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia species. It is often used in combination with beta-lactam therapy. A tobramycin minimum inhibitory concentration (MIC) of less than 4.0 mcg/mL is considered susceptible for gram-negative bacilli, while a MIC of greater than 8.0 mcg/mL is considered resistant. Toxicities include ototoxicity and nephrotoxicity. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs. Monitoring of serum levels, renal function, and symptoms consistent with ototoxicity is important. For longer durations of use, audiology and vestibular testing should be considered at baseline and periodically during therapy.

**Useful For:** Monitoring adequacy of serum concentration during tobramycin therapy

**Interpretation:** Target peak concentrations depend on the type of infection being treated. Peak levels for most infections using conventional dosing are 3.0 to 12.0 mcg/mL. Prolonged exposure to peak concentrations exceeding 12.0 mcg/mL may lead to toxicity.

**Reference Values:**
Therapeutic: 3.0-12.0 mcg/mL
Toxic: >12.0 mcg/mL


**Tobramycin, Random, Serum**

**Clinical Information:** Tobramycin is an antibiotic used to treat life-threatening blood infections caused by gram-negative bacilli, particularly Citrobacter freundii, Enterobacter (all species), Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia. It is often used in combination with beta-lactam therapy. A tobramycin minimum inhibitory concentration (MIC) of less than 4.0 mcg/mL is considered susceptible for gram-negative bacilli, while a MIC of greater than 8.0 mcg/mL is considered resistant. Toxicities include ototoxicity and nephrotoxicity. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs. Monitoring of serum levels, renal function, and symptoms consistent with ototoxicity is important. For longer durations of use, audiology and vestibular testing should be considered at baseline and periodically during therapy.

**Useful For:** Monitoring adequacy of serum concentration during tobramycin therapy. This unit code is used whenever a specimen is submitted or collected without collection timing information. The phlebotomist should use this unit code if she or he does not know if this is a peak or trough specimen.

**Interpretation:** Target peak concentrations depend on the type of infection being treated. Goal trough levels should be below 2.0 mcg/mL. Concentrations refer to conventional (non-pulse) dosing. Prolonged exposure to either peak levels exceeding 12.0 mcg/mL or trough levels exceeding 2.0 mcg/mL may lead to toxicity.

**Reference Values:**
TOBRAMYCIN, PEAK
Therapeutic: 3.0-12.0 mcg/mL
Toxic: >12.0 mcg/mL

TOBRAMYCIN, TROUGH
Therapeutic: <2.0 mcg/mL
Toxic: >2.0 mcg/mL

**TOBTA 37064**

**Tobramycin, Trough, Serum**

**Clinical Information:** Tobramycin is an antibiotic used to treat life-threatening blood infections by gram-negative bacilli, particularly Citrobacter freundii, Enterobacter (all species), Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, and Serratia species. It is often used in combination with beta-lactam therapy. A tobramycin minimum inhibitory concentration (MIC) of less than 4.0 mcg/mL is considered susceptible for gram-negative bacilli, while a MIC of greater than 8.0 mcg/mL is considered resistant. Toxicities include ototoxicity and nephrotoxicity. This risk is enhanced in presence of other ototoxic or nephrotoxic drugs. Monitoring of serum levels, renal function, and symptoms consistent with ototoxicity is important. For longer durations of use, audiology and vestibular testing should be considered at baseline and periodically during therapy.

**Useful For:** Monitoring adequate clearance of tobramycin near the end of a dosing cycle

**Interpretation:** Goal levels depend on the type of infection being treated. Goal trough levels should be below 2.0 mcg/mL for conventional (nonpulse) dosing. Prolonged exposure to trough levels exceeding 2.0 mcg/mL may lead to toxicity.

**Reference Values:**
- Therapeutic: <2.0 mcg/mL
- Toxic: >2.0 mcg/mL

**Clinical References:**

**FHIPP 91121**

**Toluene as Hippuric Acid, Occupational Exposure, Urine**

**Reference Values:**

| Creatinine: | >50 mg/dL |

Hippuric Acid is a metabolite of toluene and benzyl alcohol.

**Normal (unexposed population):**
- Average 0.8 g/L

**Exposed:**

**Biological Exposure Index (BEI):**
- 1.6 g/g creatinine (toluene exposure: end of shift)

**Toxic:**
- Not established

**FFTTLB 91141**

**Toluene, Occupational Exposure, Blood**

**Reference Values:**

| Units: | mg/L |

Normal (unexposed population): None detected
Exposed:
Biological Exposure Index (BEI): 0.05 mg/L (prior to last shift of workweek)
Biological Tolerance Value (BAT): 1.0 mg/L (end of exposure or end of shift)

Toxic:
Blood levels between 50 and 79 mg/L were found in people who died of acute toluene inhalation.

**Toluene, Occupational Exposure, Serum**

**Reference Values:**
Report limit: 0.02 mg/L

- Normal (Unexposed Population):
  - None Detected
- Exposed:
  - Not Established
- Toxic:
  - Not Established

**Tomato IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Tomato, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased
likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>Interpretation</th>
<th>Reference Values apply to all ages.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>


### Topiramate, Serum

**Clinical Information:** Topiramate is a broad spectrum, antiepileptic drug used for various types of seizures, Lennox-Gastaut syndrome (a type of childhood onset epilepsy), and migraine prophylaxis. Topiramate blocks voltage-dependent sodium channels, potentiates gamma-aminobutyric acid (GABA) activity at some of the GABA receptors, and inhibits potentiation of the glutamate receptor and carbonic anhydrase enzyme, which all contribute to its antiepileptic and antimigraine efficacy. In general, topiramate shows favorable pharmacokinetics with good absorption (1-4 hours for the immediate-release formulation), low protein binding, and minimal hepatic metabolism. Elimination is predominantly renal and it is excreted unchanged in the urine with an elimination half-life of approximately 21 hours. As with other anticonvulsant drugs eliminated by the renal system, patients with impaired renal function exhibit decreased topiramate clearance and a prolonged elimination half-life. Serum concentrations of other anticonvulsant drugs are not significantly affected by the concurrent administration of topiramate with the exception of patients on phenytoin, whose serum concentrations can increase after the addition of topiramate. Other drug-drug interactions include the coadministration of phenobarbital, phenytoin, or carbamazepine, which can result in decreased topiramate concentrations. In addition, concurrent use of posaconazole and topiramate may result in the elevation of topiramate serum concentrations. Therefore, changes in cotherapy with these medications (phenytoin, carbamazepine, posaconazole, or phenobarbital) may require dose adjustment of topiramate and therapeutic drug monitoring could assist with this. The most common adverse drug effects associated with topiramate include: weight loss, loss of appetite, somnolence, dizziness, coordination problems, memory impairment, and paresthesia.

**Useful For:** Monitoring serum concentrations of topiramate Assessing compliance Assessing potential toxicity

**Interpretation:** Most individuals display optimal response to topiramate with serum levels 5.0 to 20.0 mcg/mL when used to control seizures. Some individuals may respond well outside of this range, or may display toxicity within the therapeutic range, thus interpretation should include clinical evaluation. Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next dose). Toxic levels have not been well established.

**Reference Values:**

Depends on clinical use:

Anticonvulsant: 5.0-20.0 mcg/mL
Psychiatric: 2.0-8.0 mcg/mL


TRCHG

61859

ToRCH Profile IgG, Serum

Clinical Information: Toxoplasma gondii: Toxoplasma gondii is an obligate intracellular protozoan parasite that is capable of infecting a variety of intermediate hosts including humans. Infected definitive hosts (cats) shed oocysts in feces that rapidly mature in the soil and become infectious.(1) Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital Toxoplasmosis. Following primary infection, Toxoplasma gondii can remain latent for the life of the host; the risk for reactivation is highest among immunosuppressed individuals. Seroprevalence studies performed in the United States indicate that approximately 9% to 11% of individuals between the ages of 6 and 49 have antibodies to Toxoplasma gondii.(2) Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most commonly present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS or individuals that are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involved the central nervous system.(3) Transplacental transmission of the parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation.(4) The incidence of congenital toxoplasmosis increases as pregnancy progresses; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. A majority of infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero; approximately 10% exhibit ocular involvement only and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual and audiologic defects. Rubella: Rubella (German or 3-day measles) is a member of the togavirus family and humans remain the only natural host for this virus. Transmission is typically through inhalation of infectious aerosolized respiratory droplets and the incubation period following exposure can range from 12 to 23 days.(5) Infection is generally mild and self-limited, and is characterized by a maculopapular rash beginning on the face and spreading to the trunk and extremities, fever, malaise, and lymphadenopathy.(6) Primary, in utero rubella infections can lead to severe sequelae for the fetus, particularly if infection occurs within the first 4 months of gestation. Congenital rubella syndrome is often associated with hearing loss, cardiovascular and ocular defects.(7) The United States 2-dose measles, mumps, rubella (MMR) vaccination program, which calls for vaccination of all children, may result in premature delivery and subsequent neurologic, intellectual and audiologic defects. Rubella: Rubella (German or 3-day measles) is a member of the togavirus family and humans remain the only natural host for this virus. Transmission is typically through inhalation of infectious aerosolized respiratory droplets and the incubation period following exposure can range from 12 to 23 days.(5) Infection is generally mild and self-limited, and is characterized by a maculopapular rash beginning on the face and spreading to the trunk and extremities, fever, malaise, and lymphadenopathy.(6) Primary, in utero rubella infections can lead to severe sequelae for the fetus, particularly if infection occurs within the first 4 months of gestation. Congenital rubella syndrome is often associated with hearing loss, cardiovascular and ocular defects.(7) The United States 2-dose measles, mumps, rubella (MMR) vaccination program, which calls for vaccination of all children, leads to seroconversion in 95% of children following the first dose.(5) A total of 4 cases of rubella were reported to the CDC in 2011 without any cases of congenital rubella syndrome.(8) Due to the success of the national vaccination program, rubella is no longer considered endemic in the United States (cdc.gov/rubella). Immunity may however wane with age as approximately 80% to 90% of adults will show serologic evidence of immunity to rubella. Cytomegalovirus (CMV): CMV is a member of the Herpesviridae family of viruses and usually causes asymptomatic infection after which it remains latent in patients, primarily within bone marrow derived cells.(9) Primary CMV infection in immunocompetent individuals may also manifest as a mononucleosis-type syndrome, similar to primary Epstein-Barr virus infection, with fever, malaise, and lymphadenopathy. CMV is a significant cause of morbidity and mortality among bone marrow or solid organ transplant recipients, individuals with AIDS and other immunosuppressed patients due to virus reactivation, or from a newly acquired infection.(10,11) Infection in these patient populations can affect...
almost any organ and lead to multi-organ failure. CMV is also responsible for congenital disease among newborns and is 1 of the ToRCH infections (toxoplasmosis, other infections including syphilis, rubella, CMV, and herpes simplex virus [HSV]). CMV seroprevalence increases with age. In the United States the prevalence of CMV-specific antibodies increases from approximately 36% to over 91% in adolescents between the ages of 6 and 11 and adults over 80 years old, respectively.(12) Herpes Simplex Virus (HSV) Types 1 and 2: HSV types 1 and 2 are members of the Herpesviridae, and produce infections that may range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV types 1 and 2 can differ significantly in their clinical manifestations and severity. HSV type 2 primarily causes urogenital infections and is found almost exclusively in adults. HSV type 1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. The diagnosis HSV infections is routinely made based on clinical findings and supported by laboratory testing using PCR or viral culture. However, in instances of subclinical or unrecognized HSV infection, serologic testing for IgG-class antibodies to type-specific HSV glycoprotein G (gG) may be useful. There are several circumstances in which it may be important to distinguish between infection caused by HSV types 1 and 2.(13) For example, the risk for reactivation is highest for HSV type 2 and the method of antiviral therapy may be different depending on the specific type of HSV causing disease. In addition, the results of HSV type specific IgG testing is sometimes used during pregnancy to identify risks of congenital HSV disease and allow for focused counseling prior to delivery.(14,15)

Useful For: Determination of immune status of individuals to the rubella virus following vaccination or prior exposure As an indication of past or recent infection with Toxoplasma gondii, cytomegalovirus, or herpes simplex virus (HSV) Distinguishing between infection caused by HSV types 1 and 2, especially in patients with subclinical or unrecognized HSV infection

Interpretation: Toxoplasma gondii: A positive Toxoplasma IgG result is indicative of current or past infection with Toxoplasma gondii. A single positive Toxoplasma IgG result should not be used to diagnose recent infection. Equivocal Toxoplasma IgG results may be due to very low levels of circulating IgG during the acute stage of infection. A second specimen should be submitted for testing if clinically indicated. Individuals with negative Toxoplasma IgG results are presumed to not have had previous exposure to Toxoplasma gondii. However, negative results may be seen in cases of remote exposure with subsequent loss of detectable antibody. Seroconversion from negative to positive IgG is indicative of Toxoplasma gondii infection subsequent to the first negative specimen. Recent or acute infection with Toxoplasma gondii can be evaluated with TOXMP / Toxoplasma gondii Antibody, IgM, Serum assay. Rubella: Positive: The presence of detectable IgG-class antibodies to rubella indicates prior exposure through infection or immunization. Individuals testing positive for IgG-class antibodies to rubella are considered immune. Equivocal: Submit an additional specimen for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative: The absence of detectable IgG-class antibodies to rubella suggests no prior exposure to this virus or the lack of a specific immune response to immunization. Cytomegalovirus (CMV): Positive CMV IgG results indicate past or recent CMV infection. These individuals may transmit CMV to susceptible individuals through blood and tissue products. Equivocal CMV IgG results may occur during acute infection or may be due to nonspecific binding reactions. Submit an additional specimen for testing if clinically indicated. Individuals with negative CMV IgG results are presumed to not have had prior exposure or infection with CMV, and are therefore considered susceptible to primary infection. Herpes Simplex Virus (HSV): The presence of IgG-class antibodies to HSV types 1 or 2 indicates previous exposure, and does not necessarily indicate that HSV is the causative agent of an acute illness.

Reference Values:
Toxoplasma ANTIBODY, IgG
Negative

Toxoplasma IgG
< or =9 IU/mL (Negative)
10-11 IU/mL (Equivocal)
> or =12 IU/mL (Positive)
RUBELLA ANTIBODY, IgG
Vaccinated: Positive (≥ 1.0 AI)
Unvaccinated: Negative (≤ 0.7 AI)

CYTOMEGALOVIRUS
Negative

HERPES SIMPLEX VIRUS (HSV), TYPE 1 AND TYPE 2 ANTIBODIES, IgG
Herpes Simplex Virus (HSV) Type 1, IgG
Negative

Herpes Simplex Virus (HSV) Type 2, IgG
Negative

Clinical References:


Clinical Information:

Toxoplasma gondii: Toxoplasma gondii is an obligate intracellular protozoan parasite that is capable of infecting a variety of intermediate hosts including humans. Infected definitive hosts (cats) shed oocysts in feces that rapidly mature in the soil and become infectious. Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital toxoplasmosis. Following primary infection Toxoplasma gondii can remain latent for the life of the host; the risk for reactivation is highest among immunosuppressed individuals. Seroprevalence studies performed in the United States indicate that approximately 6.7% of individuals between the ages of 12 and 49 have antibodies to Toxoplasma gondii. Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most commonly present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS or individuals who are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involved the central nervous system. Transplacental transmission of the parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation. The incidence of congenital toxoplasmosis increases as pregnancy advances.
Infections; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. A majority of infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero; approximately 10% exhibit ocular involvement only and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual, and audiologic defects. Cytomegalovirus (CMV): CMV is a member of the Herpesviridae family of viruses and usually causes asymptomatic infection after which it remains latent in patients, primarily within bone marrow derived cells. Primary CMV infection in immunocompetent individuals may also manifest as a mononucleosis-type syndrome, similar to primary Epstein-Barr virus infection, with fever, malaise, and lymphadenopathy. CMV is a significant cause of morbidity and mortality among bone marrow or solid organ transplant recipients, individuals with AIDS, and other immunosuppressed patients due to virus reactivation or from a newly acquired infection. Infection in these patient populations can affect almost any organ and lead to multiorgan failure. CMV is also responsible for congenital disease among newborns and is one of the ToRCH infections (toxoplasmosis, other infections including syphilis, rubella, CMV, and herpes simplex virus: HSV). CMV seroprevalence increases with age. In the United States, the prevalence of CMV-specific antibodies increases from approximately 36% to over 91% in adolescents between the ages of 6 through 11 and adults over 80 years old, respectively. Herpes Simplex Virus (HSV): HSV types 1 and 2 are members of the Herpesviridae family of viruses and produce infections that may range from mild stomatitis to disseminated and fatal disease. Clinical conditions associated with HSV infection include gingivostomatitis, keratitis, encephalitis, vesicular skin eruptions, aseptic meningitis, neonatal herpes, genital tract infections, and disseminated primary infection. Infections with HSV types 1 and 2 can differ significantly in their clinical manifestations and severity. HSV type 2 primarily causes urogenital infections and is found almost exclusively in adults. HSV type 1 is closely associated with orolabial infection, although genital infection with this virus can be common in certain populations. The diagnosis of HSV infections are routinely made based on clinical findings and supported by laboratory testing using PCR or viral culture. However, in instances of subclinical or unrecognized HSV infection, serologic testing for IgG-class antibodies to type-specific HSV glycoprotein G (gG) may be useful. There are several circumstances in which it may be important to distinguish between infection caused by HSV types 1 and 2. For example, the risk for reactivation is highest for HSV type 2 and the method of antiviral therapy may differ depending on the specific type of HSV-causing disease. In addition, the results of HSV type-specific IgG testing is sometimes used during pregnancy to identify risks of congenital HSV disease and allow for focused counseling prior to delivery.

**Useful For:** Aiding in the diagnosis of acute or recent infection with Toxoplasma gondii, cytomegalovirus, or herpes simplex virus

**Interpretation:** Toxoplasma gondii: Diagnosis of acute central nervous system, intrauterine, or congenital toxoplasmosis is difficult by routine serological methods. Active toxoplasmosis is suggested by the presence of IgM antibodies, but elevated anti-IgM titers are often absent in immunocompromised patients. In addition, elevated IgM can persist from an acute infection that may have occurred as long ago as 1 year. A suspected diagnosis of acute toxoplasmosis should be confirmed by further testing at a toxoplasmosis reference laboratory or by detection of Toxoplasma gondii DNA by PCR analysis of cerebrospinal fluid or amniotic fluid specimens (PTOX / Toxoplasma gondii, Molecular Detection, PCR). For confirmation of toxoplasmosis, the FDA issued a Public Health Advisory (7/25/1997) that recommends that sera found to be positive for Toxoplasma gondii IgM antibodies should be sent to a Toxoplasma reference laboratory. Specimens interpreted as equivocal may contain very low levels of IgM. A second specimen should be drawn and tested. Cytomegalovirus (CMV): A negative CMV IgM result suggests that the patient is not experiencing an acute or active infection. However, a negative result does not rule-out primary CMV infection. It has been reported that CMV-specific IgM antibodies were not detectable in 10% to 30% of cord blood sera from infants demonstrating infection in the first week of life. In addition, up to 23% (3/13) of pregnant women with primary CMV infection did not demonstrate detectable CMV IgM responses within 8 weeks postinfection. In cases of primary infection, where the time of seroconversion is not well defined, as high as 28% (10/36) of pregnant women did not demonstrate CMV IgM antibody. Positive CMV IgM results indicate a recent infection (primary, reactivation, or reinfection). IgM antibody responses in secondary (reactivation) CMV infections have been demonstrated in some CMV mononucleosis patients, in a few pregnant women, and in renal and
cardiac transplant patients. Levels of antibody may be lower in transplant patients with secondary rather than primary infections. Equivocal CMV IgM or IgG results may occur during acute infection or may be due to nonspecific binding reactions. Submit an additional sample for testing if clinically indicated.

Herpes Simplex Virus (HSV): The presence of IgM-class antibodies indicates recent infection. A negative result does not exclude the possibility of active disease. If lesions are present, a dermal swab and submission for HSV PCR is recommended.

Reference Values:

**TOXOPLASMA ANTIBODY, IgM**
Negative

**CYTOMEGALOVIRUS, IgM**
Negative

**HERPES SIMPLEX VIRUS, IgM**
Negative

Reference values apply to all ages.

Clinical References:

**FFTOX**

**Toxocara Antibody, ELISA (Serum)**

Reference Values:
REFERENCE RANGE: Negative

Results of this assay must be interpreted with caution, as broad variations in antibody response occur, and levels may remain elevated for years after infection. Further, as with many parasitic serology assays, antibodies induced by other parasitic infections may crossreact in this assay. Although a negative result usually rules out infection with Toxocara spp., parallel testing of serial samples may prove useful in following patients with suspected Toxocara infection.

**TOXGP**

**Toxoplasma gondii Antibody, IgG, Serum**

Clinical Information: Toxoplasma gondii is an obligate intracellular protozoan parasite that is capable of infecting a variety of intermediate hosts including humans. Infected definitive hosts (cats)
shed oocysts in feces that rapidly mature in the soil and become infectious. (1) Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital toxoplasmosis. Following primary infection, Toxoplasma gondii can remain latent for the life of the host; the risk for reactivation is highest among immunosuppressed individuals. Seroprevalence studies performed in the United States indicate that approximately 9% to 11% of individuals between the ages of 6 and 49 have antibodies to Toxoplasma gondii. (2) Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most commonly present with lymphadenopathy and other non-specific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS or individuals who are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involved the central nervous system. (3) Transplacental transmission of the parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation. (4) The incidence of congenital toxoplasmosis increases as pregnancy progresses; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. A majority of infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero; approximately 10% exhibit ocular involvement only and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual, and audiologic defects.

**Useful For:** Determining whether a patient has had previous exposure to or recent infection with Toxoplasma gondii

**Interpretation:** A positive Toxoplasma IgG result is indicative of current or past infection with Toxoplasma gondii. A single positive Toxoplasma IgG result should not be used to diagnose recent infection. Equivocal Toxoplasma IgG results may be due to very low levels of circulating IgG during the acute stage of infection. A second specimen should be submitted for testing if clinically indicated. Individuals with negative Toxoplasma IgG results are presumed to not have had previous exposure to Toxoplasma gondii. However, negative results may be seen in cases of remote exposure with subsequent loss of detectable antibody. Seroconversion from negative to positive IgG is indicative of Toxoplasma gondii infection subsequent to the first negative specimen. Recent or acute infection with Toxoplasma gondii can be evaluated with the TOXMP/Toxoplasma gondii Antibody, IgM, Serum assay. A suspected diagnosis of acute toxoplasmosis should be confirmed by detection of Toxoplasma gondii DNA by PCR analysis of cerebrospinal fluid or amniotic fluid specimens (PTOX/Toxoplasma gondii, Molecular Detection, PCR). For further confirmation of a diagnosis, the FDA issued a Public Health Advisory (7/25/1997) suggesting that sera found to be positive/equivocal for Toxoplasma gondii IgM antibody be sent to a Toxoplasma reference laboratory. Recommended laboratories included the CDC or Jack Remington MD, Palo Alto Medical Foundation, 860 Bryant St., Palo Alto, CA 94301.

**Reference Values:**

Toxoplasma ANTIBODY, IgG

- Negative

<table>
<thead>
<tr>
<th>Toxoplasma IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; or =9 IU/mL (Negative)</td>
</tr>
<tr>
<td>10-11 IU/mL (Equivocal)</td>
</tr>
<tr>
<td>&gt; or =12 IU/mL (Positive)</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

Toxoplasma gondii Antibody, IgM and IgG (Separate Determinations), Serum

**Clinical Information:** Toxoplasma gondii is an obligate intracellular protozoan parasite that is capable of infecting a variety of intermediate hosts including humans. Infected definitive hosts (cats) shed oocysts in feces that rapidly mature in the soil and become infectious. Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital toxoplasmosis. Following primary infection, Toxoplasma gondii can remain latent for the life of the host; the risk for reactivation is highest among immunosuppressed individuals. Seroprevalence studies performed in the United States indicate that approximately 6.7% of individuals between the ages of 12 and 49 have antibodies to Toxoplasma gondii. Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most commonly present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS or individuals who are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involved the central nervous system. Transplacental transmission of the parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation. The incidence of congenital toxoplasmosis increases as pregnancy progresses; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. A majority of infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero; approximately 10% exhibit ocular involvement only and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual, and audiologic defects.

**Useful For:** Determining whether a patient has had previous exposure to or recent infection with Toxoplasma gondii

**Interpretation:** Active toxoplasmosis is suggested by the presence of IgM-class antibodies, but elevated anti-IgM titers may be absent in immunocompromised patients. In addition, elevated IgM can persist from an acute infection that may have occurred as long ago as 1 year. A suspected diagnosis of acute toxoplasmosis should be confirmed by detection of Toxoplasma gondii DNA by PCR analysis of cerebrospinal fluid or amniotic fluid specimens (PTOX / Toxoplasma gondii, Molecular Detection, PCR). For confirmation of toxoplasmosis, the FDA issued a Public Health Advisory (7/25/1997) that recommends that sera found to be positive for Toxoplasma gondii IgM antibodies should be sent to a Toxoplasma reference laboratory. A single negative result should not be used to rule-out toxoplasmosis and repeat testing is recommended for patients at high risk for infection. IgG is only indicative of previous exposure to Toxoplasma (recent or past). A single positive Toxoplasma IgG result should not be used to diagnose recent infection. Seroconversion from negative to positive IgG is indicative of recent Toxoplasma gondii infection.

**Reference Values:**

<table>
<thead>
<tr>
<th>Toxoplasma IgM</th>
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<tr>
<td>Toxoplasma IgG</td>
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</table>

**Toxoplasma IgG Value**

<table>
<thead>
<tr>
<th>Value</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 9 IU/mL</td>
<td>Negative</td>
</tr>
<tr>
<td>10-11 IU/mL</td>
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</tr>
<tr>
<td>≥ 12 IU/mL</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.

**Clinical References:** 1. Tenter AM, Heckerth AR, Weiss LM: Toxoplasma gondii: from animals
Toxoplasma gondii Antibody, IgM, Serum

**Clinical Information:** Toxoplasma gondii is an obligate intracellular protozoan parasite that is capable of infecting a variety of intermediate hosts including humans. Infected definitive hosts (cats) shed oocysts in feces that rapidly mature in the soil and become infectious. Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital toxoplasmosis. Following primary infection, Toxoplasma gondii can remain latent for the life of the host; the risk for reactivation is highest among immunosuppressed individuals. Seroprevalence studies performed in the United States indicate that approximately 6.7% of individuals between the ages of 12 and 49 have antibodies to Toxoplasma gondii. Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most commonly present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS or individuals that are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involved the central nervous system. Transplacental transmission of the parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation. The incidence of congenital toxoplasmosis increases as pregnancy progresses; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. A majority of infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero; approximately 10% exhibit ocular involvement only and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual and audiologic defects.

**Useful For:** Detection of recent infection with Toxoplasma gondii

**Interpretation:** Active toxoplasmosis is suggested by the presence of IgM-class antibodies, but elevated anti-IgM titers may be absent in immunocompromised patients. In addition, elevated IgM can persist from an acute infection that may have occurred as long ago as 1 year. A suspected diagnosis of acute toxoplasmosis should be confirmed by detection of Toxoplasma gondii DNA by PCR analysis of cerebrospinal fluid or amniotic fluid specimens (PTOX / Toxoplasma gondii, Molecular Detection, PCR). For confirmation of toxoplasmosis, the FDA issued a Public Health Advisory (7/25/1997) that recommends that sera found to be positive for Toxoplasma gondii IgM antibodies should be sent to a Toxoplasma reference laboratory. A single negative result should not be used to rule-out toxoplasmosis and repeat testing is recommended for patients at high risk for infection.

**Reference Values:**

**Negative**
- Reference values apply to all ages.

**Clinical References:**
Toxoplasma Gondii IgG and IgM, CSF

Reference Values:

Reference Range:

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<th>interpretation</th>
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<td>&gt; or =1.10</td>
<td>Antibody detected</td>
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<tr>
<td>IgM</td>
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<td></td>
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<tr>
<td></td>
<td>&gt; or =1.00</td>
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</tbody>
</table>

INTERPRETIVE CRITERIA:

Diagnosis of central nervous system infections can be accomplished by demonstrating the presence of intrathecally-produced specific antibody. Interpreting results may be complicated by low antibody levels found in CSF, passive transfer of antibody form blood, and contamination via bloody taps. The interpretation of CSF results must consider CSF-serum antibody ratios to the infectious agent.

Toxoplasma gondii, Molecular Detection, PCR

Clinical Information: Toxoplasma gondii is an obligate intracellular protozoan parasite that is capable of infecting a variety of intermediate hosts including humans. Infected definitive hosts (cats) shed oocysts in feces that rapidly mature in the soil and become infectious.(1) Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital toxoplasmosis. Following primary infection, T gondii can remain latent for the life of the host; the risk for reactivation is highest among immunosuppressed individuals. Seroprevalence studies performed in the United States indicate that approximately 9% to 11% of individuals between the ages of 6 and 49 have antibodies to T gondii.(2) Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most commonly present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS or individuals who are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involved the central nervous system.(3) Transplacental transmission of the parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation.(4) The incidence of congenital toxoplasmosis increases as pregnancy progresses; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. A majority of infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero; approximately 10% exhibit ocular involvement only and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual, and audiologic defects. Serology is the traditional method for diagnosing toxoplasmosis and ascertaining the previous exposure history of the host. However, serology may be unreliable or challenging to interpret in immunocompromised patients and in suspected intrauterine infection. Detection of T gondii DNA by PCR has proven to be a rapid and reliable alternative or supportive method for the diagnosis of toxoplasmosis.
Useful For: Supporting the diagnosis of acute cerebral, ocular, disseminated, or congenital toxoplasmosis

Interpretation: A positive result indicates presence of DNA from Toxoplasma gondii. Negative results indicate absence of detectable DNA but do not exclude the presence of organism or active or recent disease.

Reference Values:
Negative


Toxoplasma gondii, Molecular Detection, PCR, Blood

Clinical Information: Toxoplasma gondii is an obligate intracellular protozoan parasite that is capable of infecting a variety of intermediate hosts including humans. Infected definitive hosts (cats) shed oocysts in feces that rapidly mature in the soil and become infectious.(1) Toxoplasmosis is acquired by humans through ingestion of food or water contaminated with cat feces or through eating undercooked meat containing viable oocysts. Vertical transmission of the parasite through the placenta can also occur, leading to congenital toxoplasmosis. Following primary infection, T. gondii can remain latent for the life of the host; the risk for reactivation is highest among immunosuppressed individuals. Seroprevalence studies performed in the United States indicate that approximately 9% to 11% of individuals between the ages of 6 and 49 have antibodies to T. gondii.(2) Infection of immunocompetent adults is typically asymptomatic. In symptomatic cases, patients most commonly present with lymphadenopathy and other nonspecific constitutional symptoms, making definitive diagnosis difficult to determine. Severe-to-fatal infections can occur among patients with AIDS or individuals who are otherwise immunosuppressed. These infections are thought to be caused by reactivation of latent infections and commonly involved the central nervous system.(3) Transplacental transmission of the parasites resulting in congenital toxoplasmosis can occur during the acute phase of acquired maternal infection. The risk of fetal infection is a function of the time at which acute maternal infection occurs during gestation.(4) The incidence of congenital toxoplasmosis increases as pregnancy progresses; conversely, the severity of congenital toxoplasmosis is greatest when maternal infection is acquired early during pregnancy. A majority of infants infected in utero are asymptomatic at birth, particularly if maternal infection occurs during the third trimester, with sequelae appearing later in life. Congenital toxoplasmosis results in severe generalized or neurologic disease in about 20% to 30% of the infants infected in utero; approximately 10% exhibit ocular involvement only and the remainder are asymptomatic at birth. Subclinical infection may result in premature delivery and subsequent neurologic, intellectual, and audiologic defects. Detection of T. gondii DNA by PCR has proven to be a rapid and reliable alternative or supportive method for the diagnosis of toxoplasmosis. When performed on blood, it may detect circulating parasite DNA and thus confirm or support the results of serologic testing. PCR testing on peripheral blood has been used successfully to detect cases of ocular toxoplasmosis(2) as well as invasive disease in allogeneic stem cell recipients.(3,4) However, blood may not be a sensitive specimen for detecting organ specific disease (eg, ocular or cerebral toxoplasmosis). In this case, other specimens (eg, ocular fluid, CSF, fresh tissue) should be considered (order PTOX / Toxoplasma gondii, Molecular Detection, PCR).

Useful For: Supporting the diagnosis of active toxoplasmosis, particularly in immunocompromised individuals

Interpretation: A positive result indicates presence of DNA from Toxoplasma gondii. Negative results indicate absence of detectable DNA, but do not exclude the presence of organism or active or recent
Reference Values:
Negative

Clinical References:

Toxoplasma Immunostain, Technical Component Only

Clinical Information: Immunohistochemical staining for Toxoplasma gondii can help identify the organisms in the cytoplasm of infected cells. T. gondii is a sporozoan that lives as an intracellular parasite in various tissues of vertebrates. T. gondii is transmitted via raw or undercooked meat, contaminated soil, or by direct contact. Pregnant women and immunosuppressed patients are at highest risk for infection.

Useful For: Aids in the identification of Toxoplasma gondii infection

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

TP53 Gene, Full Gene Analysis

Clinical Information: Li-Fraumeni syndrome (LFS) is a rare autosomal dominant hereditary cancer syndrome associated with germline mutations in the TP53 (also p53) gene. LFS is predominantly characterized by sarcoma (osteogenic, chondrosarcoma, rhabdomyosarcoma), young-onset breast cancer, brain cancer (glioblastoma), hematopoietic malignancies, and adrenocortical carcinoma in affected individuals. LFS is highly penetrant; the risk for developing an invasive cancer is 50% by age 30 and 90% by age 70 with many individuals developing multiple primary cancers. Childhood cancers are also frequently observed and typically include soft-tissue sarcomas, adrenocortical tumors, and brain cancer. Other reported malignancies include melanoma, Wilms tumor, kidney tumors, gonadal germ cell tumor, pancreatic cancer, gastric cancer, choroid plexus cancer, colorectal cancer, prostate cancer, endometrial cancer, esophageal cancer, lung cancer, ovarian cancer, and thyroid cancer. There are published criteria for the use in establishing a clinical diagnosis of classic Li-Fraumeni syndrome and Li-Fraumeni-like (LFL) syndrome that include the above features listed. A larger percentage of families...
that meet the classic LFS criteria, are predicted to have a detectable mutation within the TP53 gene than families that meet the less strict LFL criteria (Birch's and Eeles' definitions).

**Useful For:** Confirmation of suspected clinical diagnosis of Li-Fraumeni syndrome or Li-Fraumeni-like syndrome Identification of familial TP53 mutation to allow for predictive testing in family members

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Tragacanth, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<td>3</td>
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**TRAM**

**Tramadol and Metabolite, Random Urine**

**Clinical Information:** Tramadol, a centrally acting opioid analgesic, is utilized in the treatment of moderate to moderately severe pain. Tramadol acts as an opiate agonist through the binding of the parent drug and its O-desmethyl (M1) metabolite to mu-opioid receptors and through the weak inhibition of norepinephrine and serotonin reuptake. The active metabolite, O-desmethyltramadol, is a considerably more potent mu-opioid receptor agonist than its parent drug. In urine, approximately 30% of tramadol is excreted as unchanged drug, while approximately 60% is excreted as metabolites (N- and O-desmethyltramadol). The half-life of tramadol and O-desmethyltramadol is approximately 7 hours.

**Useful For:** Monitoring of compliance utilizing tramadol Detection and confirmation of the illicit use of tramadol

**Interpretation:** The presence of tramadol or O-desmethyltramadol levels of 25 ng/mL or higher is a strong indicator that the patient has used tramadol.

**Reference Values:**
Cutoff: 25 ng/mL


**TFE3I**

**Transcription Factor E3 (TFE3) Immunostain, Technical Component Only**

**Clinical Information:** Transcription factor E3 (TFE3) is a member of the microphthalmia transcription factor (MiTF)/TFE family of helix-loop-helix transcription factors. TFE3 overexpression is observed in TFE translocation-associated renal cell carcinoma and alveolar soft part sarcoma.

**Useful For:** Assessment of transcription factor E3 expression

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Transferrin, Serum

**Clinical Information:** Transferrin is a glycoprotein with a molecular weight of 79570 daltons. It consists of a polypeptide strand with 2 N-glycosidically linked oligosaccharide chains and exists in numerous isoforms. The rate of synthesis in the liver can be altered in accordance with the body’s iron requirements and iron reserves. Transferrin is the iron transport protein in serum. In cases of iron deficiency, the degree of transferrin saturation appears to be an extremely sensitive indicator of functional iron depletion. The ferritin levels are depressed when there is a deficiency of storage iron. In sideropenia, an iron deficiency can be excluded if the serum transferrin concentration is low, as in inflammation or less commonly, in cases of ascorbic acid deficiency. In screening for hereditary hemochromatosis, transferrin saturation provides a better indication of the homozygous genotype than does ferritin. The treatment of anemia with erythropoietin in patients with renal failure is only effective when sufficient depot iron is present. The best monitoring procedure is to determine transferrin saturation during therapy. Transferrin saturation in conjunction with ferritin gives a conclusive prediction of the exclusion of iron overloading in patients with chronic liver disease.

**Useful For:** Screening for chronic iron overload diseases, particularly hereditary hemochromatosis

**Interpretation:** Serum iron, total iron-binding capacity (TIBC), and percent saturation are useful only in screening for chronic iron overload diseases, particularly hereditary hemochromatosis. Although serum iron, TIBC, and percent saturation are widely used for the diagnosis of iron deficiency, serum ferritin is a much more sensitive and reliable means of demonstrating iron deficiency. In hereditary hemochromatosis, serum iron is usually above 150 mcg/dL and percent saturation exceeds 60%. In advanced iron overload states, the percent saturation often exceeds 90%.

**Reference Values:**
200-360 mg/dL

**Clinical References:**

Transforming Growth Factor beta, Serum

**Interpretation:** Results are intended for research purposes or in attempts to understand the pathophysiology of unusual immune or inflammatory disorders.

**Reference Values:**
Transforming Growth Factor beta, S: 3,465 â€“ 13,889 pg/mL

Transmembrane Activator and CAML Interactor (TACI) Gene, Full Gene Analysis
Clinical Information: Transmembrane activator and CAML interactor (TACI) is a member of the tumor-necrosis factor (TNF)-like receptor family, a group of receptors that regulate both survival and apoptosis of immune cells.(1) TACI is encoded by the TACI gene (official symbol, TNFRSF13B). TACI is expressed on the surface of resting B cells and activated T cells, but not resting T cells. TACI interacts with 2 ligands-BAFF (B-cell activating factor), also known as BLys (B-lymphocyte stimulator), which belongs to the TNF family, and APRIL (a proliferation-inducing ligand). The ligands for TACI are expressed on macrophages, monocytes, and dendritic cells.(2) TACI regulates isotype class-switching of immunoglobulins and also is involved in the antibody response to T-independent antigens.(3) The human TACI gene locus is located on the short arm of chromosome 17, which is a common target for variation and rearrangement.(3) The TACI gene consists of 5 exons spanning approximately 35 kb (including 1002 bp upstream of the 5' untranslated region [UTR] and 1024 bp downstream of the 3' UTR). In recent studies, 4 variants (p.L69Tfs*12, p.C104R, p.A181E, p.R202H) have been shown to be statistically significant in common variable immunodeficiency (CVID) and selective IgA deficiency (sIgAD) patients when compared to controls.(4) Two other variants, p.P251L and p.V220A, are considered to be likely benign as they are present in both controls and patients.(4-6) The TACI gene variants described so far are nonsense, missense, or frameshift variants, all of which can be detected by gene sequencing. CVID is a complex, heterogeneous disease with defects in 1 or more of these pathways: B-cell survival; circulating memory B cells (CD27+), including class-switched (CD27+IgM-IgD-), nonswitched (CD27+IgM+IgD+), and IgM-memory B cells (CD27+IgM+IgD-); B-cell activation after receptor cross-linking; T-cell signaling; and cytokine expression. CVID patients have hypogammaglobulinemia with impaired functional antibody responses among other clinical features. While the molecular basis for most cases of CVID and sIgAD remains unknown, a fraction of CVID cases (approximately 20%-25%) have been reported to be associated with variants in the TACI gene, ICOS, BAFF-R, or CD19. There are several other genes reported with CVID or CVID-like disease that are not discussed here. Most cases of CVID are sporadic, but at least 10% are familial with a predominance of autosomal dominant over autosomal recessive inheritance. TACI gene mutations account for 8% to 15% of CVID cases depending on the study population and are sporadic in the majority of cases. The familial TACI gene variants can be inherited in either an autosomal dominant or autosomal recessive fashion. TACI gene variants can also display incomplete penetrance, indicating that not all carriers of TACI gene variants develop the disease phenotype.(7) TACI gene variants appear to be strongly associated with lymphoproliferative diseases such as splenomegaly or tonsillar hypertrophy. Autoimmune thyroiditis is observed in 15% of TACI gene variant-positive CVID cases. Heterozygous TACI gene variants are associated with CVID and autoimmunity, while homozygous TACI gene variants appear to protect against autoimmunity (8, 9). The known TACI gene variants appear, in most cases, to be associated with normal protein expression with aberrant or absent functional activity. Consequently, the vast majority (approximately 95%) of cases cannot be identified by the flow cytometry analysis (see CVID / CVID Confirmation Flow Panel). In <5% of TACI-associated CVID cases, protein expression on B cells is absent, which can be detected by flow cytometry.(10) Therefore, in the presence of a strong clinical indication for CVID and potential TACI gene variants, such as low to absent IgA levels (in the absence of anti-IgA), lymphoproliferative disease, autoimmune thyroiditis, or autoimmune cytopenias, TACI genotyping can determine if variants are present that could explain the clinical phenotype. Genotyping can also be used to evaluate clinically symptomatic family members of patients with known TACI gene variants for correlation with clinical phenotype and genetic counseling (KVAR1 / Known Variant Analysis-1 Variant).

Useful For: Evaluating individuals with: -Common variable immunodeficiency (CVID) -Clinically symptomatic selective IgA deficiency -Lymphoproliferative disease associated with CVID -Autoimmune phenotypes with CVID These clinical features may be consistent with possible TACI variants, and the genotyping test is especially useful as a follow-up test when flow cytometry is uninformative. Identification of specific TACI variants in individuals with abnormal TACI flow cytometry results (from IABCS / B-Cell Phenotyping Profile for Immunodeficiency and Immune Competence Assessment, Blood).

Interpretation: An interpretive report is provided that describes the variants, if any, their potential clinical significance, and whether they have been previously reported or are new variants. Variants of unknown clinical significance also will be documented in the report. The published variants in the TACI gene associated with CVID are a combination of missense, nonsense, splicing, and small insertions or deletions, all of which will be detected by full gene sequencing.
**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**FFTRZ 75024**

**Trazodone (Desyrel)**

**Reference Values:**
Reference Range: 800 - 1600 ng/mL

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**FHEAV 57949**

**Tree of Heaven (Ailanthus spp) IgE**

**Interpretation:**
- Class IgE (kU/L) Comment
  - 0 <0.35 Below Detection
  - 1 0.35 – 0.69 Low Positive
  - 2 0.70 – 3.49 Moderate Positive
  - 3 3.50 – 17.49 Positive
  - 4 17.50 – 49.99 Strong Positive
  - 5 50.00 – 99.99 Very Strong Positive
  - 6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

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**TREE1 81886**

**Tree Panel # 1**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be
responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
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Reference values apply to all ages.

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Reference values apply to all ages.


Treponema pallidum Immunostain, Technical Component Only

Clinical Information: Syphilis is caused by infection with the spirochete Treponema pallidum. Transmission of T pallidum occurs via penetration of the spirochetes through mucosal membranes and abrasions on epithelial surfaces. It is primarily spread through sexual contact, but can be spread by exposure to blood products and transferred in utero.

Useful For: Identification of Treponema pallidum in tissues

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at
Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient’s clinical history and other diagnostic tests by a qualified pathologist.


**Triazolam (Halcion)**

Reference Values:
Reference Range: 5.0 - 20.0 ng/mL

**Trichinella Antibody, Serum**

Clinical Information: Trichinosis is an infection by the nematode parasite, Trichinella spiralis. The infection is acquired by ingestion of larvae in inadequately cooked, contaminated meat, especially pork, bear, and walrus meat. After ingestion, acid-pepsin digestion in the stomach liberates the larvae, which develop into adult worms in the small intestine. After fertilization, the female worm produces larvae that penetrate the mucosa and seed the skeletal muscles via the blood stream. The larvae coil and encyst in muscle fibers, remaining viable for up to several years. Diarrhea is the most common symptom associated with intestinal infection with adult worms. Fever, periorbital swelling, muscle pain and swelling, pulmonary symptoms, and rash develop during systemic invasion by the larvae.

Useful For: As an adjunct in the diagnosis of trichinosis

Interpretation: A positive ELISA result suggests current infection with Trichinella spiralis. Serology should be used in conjunction with clinical, epidemiologic, and other laboratory tests to establish the correct diagnosis. The number of individuals showing positive results may vary significantly between populations and geographic regions.

Reference Values:
Negative
Reference values apply to all ages.


**Trichloroacetic Acid, Urine**

Reference Values:
Creatinine: >50 mg/dL

Trichloroethane Exposure:
Normal (unexposed population):
None detected
Exposed:
Biological Exposure Index (BEI):
10 mg/L (end of workweek)
Toxic:
Not established

Trichloroethylene Exposure:
Normal (unexposed population):
None detected
Exposed:
Biological Exposure Index (BEI):
100 mg/g creat (end of workweek)

Biological Tolerance Value (BAT):
100 mg/L (end of exposure or end of shift, or after several shifts for long-term exposure)

Toxic:
Not established

Tetrachloroethylene (Perchloroethylene) Exposure:
Normal (unexposed population):
None detected
Exposed:
Biological Exposure Index (BEI):
7.0 mg/L (end of workweek)

Toxic:
Not established

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**Trichoderma viride, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Current as of October 11, 2018 2:20 pm CDT   800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com

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**TVRNA 61755**

**Trichomonas vaginalis by Nucleic Acid Amplification**

**Clinical Information:** Trichomonas vaginalis (TV) is a protozoan parasite that commonly infects the genital tract of men and women. It is now considered to be the most common curable sexually transmitted disease (STD) agent, with an estimated 3.7 million infected individuals in the United States.(1-4)

Although up to 70% of infected individuals are asymptomatic, infections may be associated with vaginitis, urethritis, and cervicitis in women, and urethritis and prostatitis in men.(3) Patients that are infected with Trichomonas vaginalis have an increased risk of acquiring other sexually transmitted infections such as HIV, while infections in pregnant women are associated with premature labor, low-birth-weight offspring, premature rupture of membranes, and posthysterectomy/postabortion infection.(3) Symptoms of Trichomonas vaginalis overlap considerably with other sexually transmitted infections and, therefore, laboratory diagnosis is required for definitive diagnosis. The most commonly used method for detection is microscopic examination of a wet-mount preparation of vaginal secretions. However, this method has only 35% to 80% sensitivity compared with culture.(5) Culture also suffers from relatively low sensitivity (38%-82%) when compared to molecular methods.(5) Culture is also technically challenging and takes 5 to 7 days to complete. Molecular methods, such as the APTIMA Trichomonas vaginalis Assay, offer the highest sensitivity and specificity for detection of trichomoniasis. The APTIMA test utilizes target capture, transcription-mediated amplification (TMA), and hybridization protection assay (HPA) technologies for detection of Trichomonas vaginalis ribosomal RNA (rRNA).

**Useful For:** Detection of Trichomonas vaginalis

**Interpretation:** A positive result is considered indicative of current or recent Trichomonas vaginalis infection (trichomoniasis).

**Reference Values:**

Negative

**Clinical References:**

---

**MTRNA 61756**

**Trichomonas vaginalis, Miscellaneous Sites, by Nucleic Acid Amplification**

**Clinical Information:** Trichomonas vaginalis (TV) is a protozoan parasite that commonly infects the genital tract of men and women. It is now considered to be the most common curable sexually transmitted disease (STD) agent, with an estimated 3.7 million infected individuals in the United States.(1-4)

Although up to 70% of infected individuals are asymptomatic, infections may be associated with
vaginitis, urethritis, and cervicitis in women, and urethritis and prostatitis in men. Patients that are infected with Trichomonas vaginalis have an increased risk of acquiring other sexually transmitted infections such as HIV, while infections in pregnant women are associated with premature labor, low-birth-weight offspring, premature rupture of membranes, and post-hysterectomy/post-abortion infection. Symptoms of Trichomonas vaginalis overlap considerably with other sexually transmitted infections, and therefore, laboratory diagnosis is required for definitive diagnosis. The most commonly used method for detection is microscopic examination of a wet-mount preparation of vaginal secretions. However, this method has only 35% to 80% sensitivity compared with culture. Culture also suffers from relatively low sensitivity (38%-82%) when compared to molecular methods. Culture is technically challenging and takes 5 to 7 days to complete. Molecular methods, such as the APTIMA Trichomonas vaginalis Assay, offer high sensitivity and specificity for detection of trichomoniasis. The APTIMA test utilizes target capture, transcription-mediated amplification (TMA), and hybridization protection assay (HPA) technologies for detection of Trichomonas vaginalis ribosomal RNA (rRNA).

**Useful For:** Detection of Trichomonas vaginalis

**Interpretation:** A positive result is considered indicative of current or recent Trichomonas vaginalis infection (trichomoniasis).

**Reference Values:**

**Negative**

**Clinical References:**

**Trichophyton rubrum, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
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</table>

Reference values apply to all ages.


**TRPU 82386 Trichosporon pullulans, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.
Triglycerides, Body Fluid

Clinical Information: The presence of a chylous effusion, which results from lymphatic drainage into a body cavity, can be determined by identifying triglycerides and chylomicrons in the fluid. Catheter-related iatrogenic effusions can be identified by determining the presence of intravenous solution constituents in the fluid.

Useful For: Distinguishing between chylous and nonchylous effusions Determining if bleeding has occurred in a body fluid Identifying iatrogenic effusions

Interpretation: A triglyceride concentration above 110 mg/dL is highly suggestive of a chylous effusion.

Reference Values: Not applicable


Triglycerides, CDC, Serum

Reference Values: Only orderable as part of a profile. For more information see LMPP / Lipoprotein Metabolism Profile.

Triglycerides, Non-Fasting, Serum

Clinical Information: Triglycerides are esters of the trihydric alcohol glycerol with 3 long-chain fatty acids. They are partly synthesized in the liver and partly derived from the diet. Increased plasma triglyceride levels are indicative of a metabolic abnormality and, along with elevated cholesterol, are considered a risk factor for atherosclerotic disease. Hyperlipidemia may be inherited or be associated with biliary obstruction, diabetes mellitus, nephrotic syndrome, renal failure, or metabolic disorders related to endocrinopathies. Increased triglycerides may also be medication-induced (eg, prednisone). Since cholesterol and triglycerides can vary independently, measurement of both is more meaningful than the measurement of cholesterol only See Lipids and Lipoproteins in Blood Plasma (Serum) in Special Instructions.

Useful For: Evaluation of risk factors in individuals with elevated cholesterol values

Interpretation: In the presence of other coronary heart disease risk factors, both borderline-high (150-199 mg/dL) and high values (>200 mg/dL) require attention. Triglyceride concentrations greater than 1,000 mg/dL can lead to abdominal pain and may be life-threatening due to chylomicron-induced pancreatitis.

Reference Values: The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and Non HDL cholesterol) in adults ages 18 and up:

- TRIGLYCERIDES
  - Males
    - <200 mg/dL
  - Females

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in children ages 2 to 17:

**TRIGLYCERIDES**

2-9 years:
- Acceptable: <75 mg/dL
- Borderline high: 75-99 mg/dL
- High: > or =100 mg/dL

10-17 years:
- Acceptable: <90 mg/dL
- Borderline high: 90-129 mg/dL
- High: > or =130 mg/dL

**Clinical References:**

**Triglycerides, Serum**

**Clinical Information:** Triglycerides are esters of the trihydric alcohol glycerol with 3 long-chain fatty acids. They are partly synthesized in the liver and partly derived from the diet. Increased plasma triglyceride levels are indicative of a metabolic abnormality and, along with elevated cholesterol, are considered a risk factor for atherosclerotic disease. Hyperlipidemia may be inherited or be associated with biliary obstruction, diabetes mellitus, nephrotic syndrome, renal failure, or metabolic disorders related to endocrinopathies. Increased triglycerides may also be medication-induced (eg, prednisone). Since cholesterol and triglycerides can vary independently, measurement of both is more meaningful than the measurement of cholesterol only.

**Useful For:** Evaluation of risk factors in individuals with elevated cholesterol values

**Interpretation:** In the presence of other coronary heart disease risk factors, both borderline-high (150-199 mg/dL) and high values (>200 mg/dL) require attention. Triglyceride concentrations above 1,000 mg/dL can lead to abdominal pain and may be life-threatening due to chylomicron-induced pancreatitis.

**Reference Values:**
The National Lipid Association and the National Cholesterol Education Program (NCEP) have set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and Non HDL cholesterol) in adults ages 18 and up:

**TRIGLYCERIDES**
- Normal: <150 mg/dL
- Borderline high: 150-199 mg/dL
- High: 200-499 mg/dL
- Very high: > or =500 mg/dL

The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents has set the following guidelines for lipids (total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol) in children ages 2 to 17:

**TRIGLYCERIDES**

2-9 years:
- Acceptable: <75 mg/dL
- Borderline high: 75-99 mg/dL
High: \( > \text{or} \geq 100 \text{ mg/dL} \)
10-17 years:
Acceptable: \(<90 \text{ mg/dL} \)
Borderline high: 90-129 mg/dL
High: \( > \text{or} \geq 130 \text{ mg/dL} \)

For SI unit Reference Values, see https://www.mayomedicallaboratories.com/order-tests/si-unit-conversion.html.

**Clinical References:**

**Trimellitic Anhydride, TMA, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Trimethoprim, Serum**

**Clinical Information:** Trimethoprim is coadministered with sulfamethoxazole for prophylaxis or treatment of bacterial infections. These agents are used to treat a variety of infections including methicillin-resistant Staphylococcus aureus, and for prophylaxis in immunosuppressed patients such as HIV-positive individuals. Trimethoprim has a wide therapeutic index and dose-dependent toxicity. Trimethoprim accumulates in patients with renal failure. Therapeutic drug monitoring is not commonly performed unless there are concerns about adequate absorption, clearance, or compliance. Accordingly, routine drug monitoring is not indicated in all patients.

**Useful For:** Monitoring trimethoprim therapy to ensure drug absorption, clearance, or compliance

**Interpretation:** Most patients will display peak steady state serum concentrations >2.0 mcg/mL when drawn at least 1 hour after an oral dose. Target concentrations may be higher, depending on the intent of therapy.

**Reference Values:**
>2.0 mcg/mL


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**Trimipramine, Serum**

**Clinical Information:** Trimipramine is a tricyclic antidepressant with additional anxiety-reducing sedative activity. Daily dosages for adults range from 50 mg to 300 mg and are usually divided into 2 to 3 doses per day. Therapeutic ranges are based on serum samples collected at trough (ie, immediately before the next dose). Peak serum concentrations are typically achieved after 1 to 6 hours postdosage. Common adverse effects include hypotension, tachycardia, constipation, dizziness, somnolence, and blurred vision. Risk of toxicity increases when concentrations >500 ng/mL. Serious adverse effects include coma, seizures, and QRS prolongation with ventricular dysrhythmias.

**Useful For:** Monitoring serum concentration during therapy Evaluating potential toxicity The test may also be useful to evaluate patient compliance

**Interpretation:** Most individuals display optimal response to trimipramine with serum levels of 150 to 300 ng/mL. Risk of toxicity is increased with trimipramine levels >500 ng/mL. Some individuals may respond well outside of this range, or may display toxicity within the therapeutic range; thus, interpretation should include clinical evaluation. Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next dose).

**Reference Values:** Therapeutic concentration: 150-300 ng/mL

*Note: Therapeutic ranges are for specimens drawn at trough (ie, immediately before next scheduled dose). Levels may be elevated in non-trough specimens.*
Clinical Information: The neuronal ceroid lipofuscinoses (NCL) comprise a group of recessively inherited neurodegenerative disorders involved in lysosomal protein catabolism. They are considered the most common of the neurogenetic storage disorders with incidences ranging from 1.3 to 7 per 100,000 live births. Clinically, they are characterized by vision loss, seizures, mental regression, behavioral changes, movement disorders, and the accumulation of autofluorescent storage material in the brain and tissues. Although at least 12 different genes have been identified, the NCLs have traditionally been categorized based on age of symptom onset: infantile, late-infantile, juvenile, and adult. Infantile and late-infantile NCL are caused primarily by defects in PPT1 and TPP1, respectively. Tissue damage is selective for the nervous system and many patients die in the first decade of life due to central nervous system degeneration. Children affected by infantile NCL (CLN1) typically have normal growth and development until about 6 to 12 months of age. Slowed head growth occurs at around 9 months followed by psychomotor degeneration, seizures, and progressive macular degeneration leading to blindness by the age of 2. CLN1 is caused by a deficiency of the lysosomal enzyme palmitoyl-protein thioesterase 1 (PPT1), which cleaves long-chain fatty acids (usually palmitate) from cysteine residues. Electron microscopy shows granular osmophilic deposits (GROD) in most cell types. PPT1 is thought to play an active role in various cell processes including apoptosis, endocytosis, and lipid metabolism. Infantile NCL has an incidence of 1 in 20,000 in Finland and is rare elsewhere. The late infantile form of NCL (CLN2) is primarily caused by deficiency of the lysosomal enzyme tripeptidyl peptidase 1 (TPP1), which cleaves tripeptides from the N-terminus of polypeptides. Tissue damage results from the defective degradation and consequent accumulation of storage material with a curved profile by electron microscopy. There is widespread loss of neuronal tissue especially in the cerebellum and hippocampal region. Disease onset occurs at 2 to 4 years of age with seizures, ataxia, myoclonus, psychomotor retardation, vision loss, and speech impairment. Diagnostic strategy depends on the age of onset of symptoms. In children presenting between the ages 0 to 4 years, enzyme assay of PPT1 and TPP1 is an appropriate first step. For other patients suspected of having an NCL, the molecular genetic test NCLP / Neuronal Cereoid Lipofuscinosis (NCL, Batten Disease) Panel by Next-Generation Sequencing is available.

Useful For: Evaluation of patients with clinical presentations suggestive of neuronal ceroid lipofuscinoses (NCL) Aids in the differential diagnosis of infantile and late infantile NCL when fibroblasts are available NCL testing in fibroblast specimens

Interpretation: Tripeptidyl peptidase 1 (TPP1) and palmitoyl-protein thioesterase 1 (PPT1) enzyme activity below 5 nmol/h/mg of protein are highly suggestive of late infantile and infantile neuronal ceroid lipofuscinoses (NCL), respectively.

Reference Values:
TRIPEPTIDYL PEPTIDASE 1
69-934 nmol/h/mg protein

PALMITOYL-PROTEIN THIOESTERASE 1
30-194 nmol/h/mg protein

Thioesterase 1 (PPT1), Leukocytes

Clinical Information: The neuronal ceroid lipofuscinoses (NCL) comprise a group of recessively inherited neurodegenerative disorders involved in lysosomal protein catabolism. They are considered the most common of the neurogenetic storage disorders with incidences ranging from 1.3 to 7 per 100,000 live births. Clinically they are characterized by vision loss, seizures, mental regression, behavioral changes, movement disorders, and the accumulation of autofluorescent storage material in the brain and tissues. Although at least 12 different genes have been identified, the NCL have traditionally been categorized based on the age of onset of symptoms: infantile, late-infantile, juvenile, and adult. Infantile and late-infantile NCL are caused primarily by defects in PPT1 and TPP1, respectively. Tissue damage is selective for the nervous system and many patients die in the first decade of life due to central nervous system degeneration. Children affected by infantile NCL (CLN1) typically have normal growth and development until about 6 to 12 months of age. Slowed head growth occurs at around 9 months followed by psychomotor degeneration, seizures, and progressive macular degeneration leading to blindness by the age of 2. CLN1 is caused by a deficiency of the lysosomal enzyme palmitoyl-protein thioesterase 1 (PPT1), which cleaves long-chain fatty acids (usually palmitate) from cysteine residues. Electron microscopy shows granular osmophilic deposits (GRODs) in most cell types. PPT1 is thought to play an active role in various cell processes including apoptosis, endocytosis, and lipid metabolism. Infantile NCL has an incidence of 1 in 20,000 in Finland and is rare elsewhere. The late infantile form of NCL (CLN2) is primarily caused by deficiency of the lysosomal enzyme tripeptidyl peptidase 1 (TPP1), which cleaves tripeptides from the N-terminus of polypeptides. Tissue damage results from the defective degradation and consequent accumulation of storage material with a curvilinear profile by electron microscopy. There is widespread loss of neuronal tissue especially in the cerebellum and hippocampal region. Disease onset occurs at 2 to 4 years of age with seizures, ataxia, myoclonus, psychomotor retardation, vision loss, and speech impairment. Diagnostic strategy depends on the age of onset of symptoms. In children presenting between the ages 0 to 4 years, enzyme assay of PPT1 and TPP1 is an appropriate first step. For other patients suspected of having an NCL, the molecular genetic test NCLP / Neuronal Ceroid Lipofuscinosis (NCL, Batten Disease) Panel by Next-Generation Sequencing is available.

Useful For: Evaluation of patients with clinical presentations suggestive of neuronal ceroid lipofuscinoses (NCL) Aids in the differential diagnosis of infantile and late infantile NCL

Interpretation: Tripeptidyl peptidase 1 (TPP1) and palmitoyl-protein thioesterase 1 (PPT1) enzyme activity below 5 nmol/hour/mg of protein are highly suggestive of late-infantile and infantile neuronal ceroid lipofuscinoses (NCL), respectively.

Reference Values:
TRIPEPTIDYL PEPTIDASE 1
85-326 nmol/hour/mg protein

PALMITOYL-PROTEIN THIOESTERASE 1
20-93 nmol/hour/mg protein


Trofile Co-Receptor Tropism Assay

Useful For: To determine the co-receptor tropism (CCR5, CXCR4, or dual/mixed) of a patient's HIV-1 strain for selection of CCR5 co-receptor antagonist therapy, when a patient's HIV-1 viral load is > or = 1,000 copies/mL.
**Interpretation:** CCR5 Tropic (R5) HIV-1 virus uses CCR5 to enter CD4+ cells. CXCR4 Tropic (X4) HIV-1 virus uses CXCR4 to enter CD4+ cells. DUAL/MIXED Tropic (D/M) HIV-1 dual-tropic viruses can use either CCR5 or CXCR4 to enter CD4+ cells. Mixed-tropic populations contain viruses with two or more tropisms. Non-reportable Co-receptor tropism could not be determined by the Trofile assay. Common causes of a non-reportable result are viral load <1,000 copies/mL, reduced viral fitness, or compromised sample collection/handling.

**Trofile DNA Co-Receptor Tropism Assay**

**Useful For:** To determine the co-receptor tropism (CCR5, CXCR4, or dual/mixed) of a patient’s HIV-1 strain for selection of CCR5 co-receptor antagonist therapy, when patient’s HIV-1 viral load is <1,000 copies/mL.

**Interpretation:** Trofile DNA Viral Classification CCR5 Tropic (R5) HIV-1: Virus uses CCR5 to enter CD4+ cells. CXCR4 Tropic (X4) HIV-1: Virus uses CXCR4 to enter CD4+ cells. DUAL /MIXED Tropic (D/M) HIV-1: Dual-tropic viruses can use either CXCR4 or CCR5 to enter CD4+ cells. Mixed-tropic populations contain viruses with 2 or more tropisms. Nonreportable: Co-receptor tropism could not be determined. Common causes of nonreportable results are reduced viral fitness or compromised sample handling. Please note that Trofile DNA sample collection and handling instructions differ from Trofile and other Monogram assays. Trofile uses the complete gp160 coding region of the HIV-1 envelope protein ensuring that all of the determinants of tropism are tested. Subtype is determined based on the HIV-1 gp41 envelope region.

**Tropheryma whipplei, Molecular Detection, PCR**

**Clinical Information:** Whipple disease is a chronic, systemic illness that in the majority of cases involves the small intestine and its lymphatic drainage. The disease primarily affects middle-aged individuals, with a peak incidence in the third and fourth decades. Clinical findings may include malabsorption, chronic diarrhea, abdominal pain, arthralgia, fever, and central nervous system symptoms. Pathologic changes associated with Whipple disease are distinctive, with diagnosis dependent on histologic examination of biopsy specimens from involved tissues. Electron microscopic or special high-resolution light microscopic examination of the lamina propria of the small intestine of patients with untreated Whipple disease reveals many rod-shaped bacillary organisms. These tiny bacilli, referred to as Whipple bacilli, measure about 0.25 micrometer long and are seen as periodic acid-Schiff-positive granules within macrophages. These inclusions represent fragments of the cell walls from degenerating bacilli. Culture of Whipple bacilli from biopsy material is laborious and the organism is very slow growing. Definitive identification of the Whipple associated bacillus has been difficult because of these limitations. Recently, molecular techniques using PCR and nucleotide sequencing allowed classification of this bacillus as an actinomycete not closely related to any other known species, which has been named Tropheryma whipplei.

**Useful For:** Aids in the diagnosis of Whipple disease, especially for identifying inconclusive or suspicious cases

**Interpretation:** A positive result strongly suggests a diagnosis of Whipple disease. A negative result does not negate the presence of the organism or active disease, as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of Tropheryma whipplei in quantities less than the limit of detection of the assay.

**Reference Values:**
Not applicable

**Clinical References:**
2. Morgenegg S, Dutly F, Altweeg M: Cloning and sequencing of a part of the heat shock protein 65 gene (hsp65) of "Tropheryma whippleii" and its use for detection of "T. whipplei" in clinical specimens by PCR. J Clin...
WHIPB 87974  
**Troponin I, Serum**

**Clinical Information:** Troponin is a complex that regulates the contraction of striated muscle. It consists of 3 subunits (C, T, and I) that are located periodically along the thin filament of the myofibrils. Troponin I inhibits actomyosin ATPase. Troponin I is an inhibitory protein and exhibits in 3 isoforms: cardiac muscle, slow-twitch skeletal muscle, and fast-twitch skeletal muscle. The cardiac form of troponin I has 31 amino acid residues on its N-terminal, not present in the skeletal forms, which allow for specific polyclonal and monoclonal antibody development. The cardiac specificity of this isoform improves the accuracy of diagnosis in patients with acute or chronic skeletal muscle injury and possible concomitant myocardial injury. Troponin I is the only troponin isotope present in the myocardium and is not expressed during any developmental stage in skeletal muscle. Troponin I is released into the bloodstream within hours of the onset of symptoms of myocardial infarction or ischemic damage. It can be detected at 3 to 6 hours following onset of chest pain with peak concentrations at 12 to 16 hours, and remains elevated for 5 to 9 days.

**Useful For:** Exclusion diagnosis of acute myocardial infarction

TPNI 81767

**Troponin I, Serum**

**Clinical Information:** Troponin is a complex that regulates the contraction of striated muscle. It consists of 3 subunits (C, T, and I) that are located periodically along the thin filament of the myofibrils. Troponin I inhibits actomyosin ATPase. Troponin I is an inhibitory protein and exhibits in 3 isoforms: cardiac muscle, slow-twitch skeletal muscle, and fast-twitch skeletal muscle. The cardiac form of troponin I has 31 amino acid residues on its N-terminal, not present in the skeletal forms, which allow for specific polyclonal and monoclonal antibody development. The cardiac specificity of this isoform improves the accuracy of diagnosis in patients with acute or chronic skeletal muscle injury and possible concomitant myocardial injury. Troponin I is the only troponin isotope present in the myocardium and is not expressed during any developmental stage in skeletal muscle. Troponin I is released into the bloodstream within hours of the onset of symptoms of myocardial infarction or ischemic damage. It can be detected at 3 to 6 hours following onset of chest pain with peak concentrations at 12 to 16 hours, and remains elevated for 5 to 9 days.

**Useful For:** Exclusion diagnosis of acute myocardial infarction

**Clinical Information:** Whipple disease is a chronic, systemic illness that in the majority of cases involves the small intestine and its lymphatic drainage. The disease primarily affects middle-aged individuals, with a peak incidence in the third and fourth decades. Clinical findings may include malabsorption, chronic diarrhea, abdominal pain, arthralgia, fever, and central nervous system symptoms. Pathologic changes associated with Whipple disease are distinctive, with diagnosis dependent on histologic examination of biopsy specimens from involved tissues. Electron microscopic or special high-resolution light microscopic examination of the lamina propria of the small intestine of patients with untreated Whipple disease reveals many rod-shaped bacillary organisms. These tiny bacilli, referred to as Whipple bacilli, measure about 0.25 micrometer long and are seen as periodic acid-Schiff-positive granules within macrophages. These inclusions represent fragments of the cell walls from degenerating bacilli. Culture of Whipple bacilli from biopsy material is laborious and the organism is very slow growing. Definitive identification of the Whipple-associated bacillus has been difficult because of these limitations. Recently, molecular techniques using PCR and nucleotide sequencing allowed classification of this bacillus as an actinomycete not closely related to any other known species, which has been named Tropheryma whipplei.

**Useful For:** Aids in the diagnosis of Whipple disease, especially for identifying inconclusive or suspicious cases

**Interpretation:** A positive result is considered diagnostic of Whipple disease. A negative result does not negate the presence of the organism or active disease, as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes or the presence of Tropheryma whipplei in quantities less than the limit of detection of the assay.

**Reference Values:**
Not applicable

**Interpretation:** There are, on occasions, elevations of cardiac troponin T (cTnT) which we use clinically which can be due to skeletal muscle disease. One way to unmask such elevations is to measure cardiac troponin I (cTnI), which will be normal in that circumstance. In addition, at times there are interferences that can cause spurious increases or decreases in cTnT values. Conceptually, these same interferences can occur with cTnl but in any given case, the likelihood of having both assays be confounded in that way is highly unusual. Thus, potential false-positives would be unmasked by a normal cTnI and false-negatives by an elevated value. A reference range study was conducted using the ADVIA Centaur TnI-Ultra assay based on guidance from the Clinical and Laboratory Standards Institute (CLSI) Protocol C28-A2.25. The study, which used 1,845 fresh serum, lithium heparin plasma, and EDTA plasma samples from 648 apparently healthy individuals ranging from 17 to 91 years of age, demonstrated a 99th percentile of 0.04 ng/mL (mcg/L). (1)

**Reference Values:**

< or =0.04 ng/mL

Reference values have not been established for patients <17 years of age.

**Clinical References:**

1. Package insert: Siemens Centaur XP, TnI, 04744371 Rev H, 2008-09

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**Troponin T, 5th Generation, Plasma**

**Clinical Information:** Troponin T is a myofibrillar protein found in striated musculature. There are 2 types of myofilament: a thick filament containing myosin and a thin filament consisting of 3 different proteins, namely actin, tropomyosin, and troponin. Troponin is itself a complex of 3 protein subunits, which are termed troponin T, troponin I, and troponin C: -Troponin T binds the troponin complex to tropomyosin -Troponin I inhibits actomyosin ATPase in relation to the calcium concentration -Troponin C has 4 binding sites for calcium and mediates calcium dependency Troponin T is found in free cytosol and structurally bound protein. The unbound pool of troponin T is the source of early protein release in myocardial damage. Troponin T is released from the structural elements at a later stage, corresponding to the degradation of myofibrils that occurs in irreversible myocardial damage. Troponin T becomes elevated 2 to 4 hours after the onset of myocardial necrosis and can remain elevated for up to 14 days, or even longer on occasion. The most common cause of cardiac injury is myocardial ischemia, ie, acute myocardial infarction. These patients are known to have an adverse short- and long-term prognosis compared to patients with unstable angina and no elevation of troponin T. Many of these patients, especially those with troponin T elevations above 30 ng/L, benefit from an aggressive strategy with anticoagulation and an invasive interventional strategy.

**Useful For:** Aiding in the exclusion of the diagnosis of acute coronary syndrome in a single plasma specimen Aiding in the diagnosis of acute coronary syndrome Monitoring acute coronary syndromes and estimating prognosis Possible utility in monitoring patients with nonischemic causes of cardiac injury

**Interpretation:** Values for healthy adults, based upon available literature and clinical guidelines, are 10 ng/L or less for women and 15 ng/L or less for men. For patients who present with suspected acute coronary syndromes, troponin T values greater than the reference interval with a rising (> or =10 ng/L over 2 hours or > or =12 ng/L over 6 hours) pattern are highly suggestive of acute cardiac injury. Decreasing values are indicative of recent cardiac injury. Serial measurement is highly recommended for the diagnosis or exclusion of acute coronary syndromes. Troponin T values greater than the reference interval are associated with adverse events in patients with ischemic heart disease and many other clinical situations. Clinical judgment is necessary to distinguish patients who have ischemic heart disease from those who do not.

**Reference Values:**
**TROT 82788**

**Trout, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
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</thead>
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<td>Negative</td>
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<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>

**Clinical Information:** Chagas disease (American trypanosomiasis) is an acute and chronic infection caused by the protozoan hemoflagellate, Trypanosoma cruzi, which is endemic in many areas of South and Central America. The parasite is usually transmitted by the bite of reduviid (or "kissing") bugs of the genus Triatoma, but also has been transmitted by blood transfusion, organ transplantation, and apparently also by food ingestion. The acute febrile infection is most often undiagnosed and often resolves spontaneously. The actively motile (trypomastigote) form may be demonstrated in peripheral blood by stained smears during the acute phase. Chronic infections are often asymptomatic but may progress to produce disabling and life-threatening cardiac (cardiomegaly, conduction defects) and gastrointestinal (megaeosophagus and megacolon) disease. These damaged tissues contain the intracellular amastigote of Trypanosoma cruzi. The parasite is not seen in the blood during the chronic phase. Diagnosis at this time is made by serology or tissue biopsy. A positive serology is considered presumptive evidence of active infection. Serologically positive asymptomatic persons are capable of transmitting the infection.

**Useful For:** Diagnosis of Chagas disease (infection with Trypanosoma cruzi)

**Interpretation:** A positive serology is suggestive of recent infection or past exposure. Results should be correlated with clinical presentation and other laboratory findings. Infected individuals usually begin producing antibodies to Trypanosoma cruzi during the first month following exposure to the parasite. Antibody levels may fluctuate during the chronic phase of the disease and may become undetectable after several months. Uninfected individuals are not expected to have detectable levels of antibodies to Trypanosoma cruzi.

**Reference Values:**

Negative


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**TRYPN 70572**

**Trypsin Immunostain, Technical Component Only**

**Clinical Information:** Trypsinogen is an enzyme involved in protein metabolism that is made by the acinar cells of the exocrine pancreas. After secretion into the small intestine, it is cleaved to its active form, trypsin. In normal pancreas, the antibody stains cells within acini. Ductal cells and islet cells are negative. The antibody to trypsin can be useful in classifying carcinomas of the pancreas by identifying cells with acinar differentiation. Carcinomas with ductal or endocrine differentiation will generally be negative.

**Useful For:** Identifying cells with acinar differentiation in the pancreas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:** 1. Bohe H, Bohe M, Lindstrom C, et al: Immunohistochemical

**TRPTS**

**Tryptase Immunostain, Technical Component Only**

**Clinical Information:** In normal tissues, antibodies to tryptase stain mast cells with an intense cytoplasmic granular staining pattern. This marker has great utility in supporting a diagnosis of mast cell disease.

**Useful For:** A marker of mast cells

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**TRYPA**

**Tryptase, Autopsy**

**Clinical Information:** Tryptase, a neutral protease, is present within the secretory granules of human mast cells. There are 2 forms of tryptase, designated as alpha and beta, which are encoded by 2 separate genes. Both are expressed as inactive proenzymes. Alpha-protryptase and beta-protryptase are spontaneously released from resting mast cells. The levels of the prototryptases reflect the total number of mass cells within the body, but are not an indication of mast cell activation. Beta-protryptase is processed to a mature form, which is stored in granules and released as an active tetramer that is bound to heparin or chondroitin sulfate proteoglycans. In contrast, an amino acid change in alpha-protryptase prevents processing to a mature form. Upon mast cell activation, degranulation releases mature tryptase, which is almost exclusively in the form of alpha-tryptase. After anaphylaxis, mast cell granules release tryptase; measurable amounts are found in blood, generally within 30 to 60 minutes. The levels decline under first-order kinetics with a half-life of approximately 2 hours. By comparison, histamine (another immunologic mediator released by activated mast cells) is cleared from blood within minutes. Increased serum levels may also occur after allergen challenge or in patients with systemic mastocytosis or mast cell activation syndrome.

**Useful For:** Assessing mast cell activation, which may occur as a result of anaphylaxis or allergen challenge Assessing patients with systemic mastocytosis or mast cell activation syndrome

**Interpretation:** Increased concentrations of total tryptase may indicate mast cell activation occurring
as a result of anaphylaxis or allergen challenge, or it may indicate an increased number of mast cells as seen in patients with mastocytosis. However, no specific cutoff value has been validated for autopsy specimens.

**Reference Values:**
No established reference values

**Clinical References:**

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**TRYPT (81608)**

**Tryptase, Serum**

**Clinical Information:** Tryptase, a neutral protease, is a dominant protein component of the secretory granules of human mast cells. There are 2 forms of tryptase, designated as alpha and beta, which are encoded by 2 separate genes. Both are expressed as inactive proenzymes. Alpha-protryptase and beta-protryptase are spontaneously released from resting mast cells. The levels of the protryptases reflect the total number of mass cells within the body, but are not an indication of mast cell activation. Beta-protryptase is processed to a mature form, which is stored in granules and released as an active tetramer that is bound to heparin or chondroitin sulfate proteoglycans. In contrast, an amino acid change in alpha-protryptase prevents processing to a mature form. Upon mast cell activation, degranulation releases mature tryptase, which is almost exclusively in the form of beta-tryptase. After anaphylaxis, mast cell granules release tryptase; measurable amounts are found in blood, generally within 30 to 60 minutes. The levels decline under first-order kinetics with half-life of approximately 2 hours. By comparison, histamine (another immunologic mediator released by activated mast cells) is cleared from blood within minutes. Increased serum levels may also occur after allergen challenge or in patients with systemic mastocytosis or mast cell activation syndrome.

**Useful For:** Assessing mast cell activation, which may occur as a result of anaphylaxis or allergen challenge. Assessing patients with systemic mastocytosis or mast cell activation syndrome.

**Interpretation:** Levels of total tryptase in serum > or =11.5 ng/mL may indicate mast cell activation occurring as a result of anaphylaxis or allergen challenge, or it may indicate increased number of mast cells as seen in patients with mastocytosis.

**Reference Values:**
<11.5 ng/mL

**Clinical References:**

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**TRYPP (82955)**

**Tryptophan, Plasma**

**Clinical Information:** Amino acids are the basic structural units that comprise proteins and are found throughout the body. Many inborn errors of amino acid metabolism have been identified, including glutaric acidemia type 1, which affect other metabolic activities. Amino acid disorders can manifest at any time in a person's life, but most become evident in infancy or early childhood. These disorders result in the accumulation or the deficiency of 1 or more amino acids in biological fluids, which leads to the clinical signs and symptoms of the particular amino acid disorder. Tryptophan is an essential amino acid necessary for the synthesis of serotonin, melatonin, and niacin. Low plasma concentrations of tryptophan have been associated with clinical observations of insomnia, anxiety, and depression. Glutaric acidemia type 1 is an autosomal recessive disorder of tryptophan and lysine metabolism caused by a deficiency of glutaryl-CoA dehydrogenase. Early diagnosis and treatment is essential to help prevent encephalopathic crises leading to brain degeneration. These can be provoked...
by infections, trauma, fever, and fasting. Treatment consists of preventing neurodegeneration through strict adherence to an emergency protocol. Dietary protein, in particular, lysine, is restricted during the vulnerable period of brain development from 0 to 5 years of age. In addition to other indices of malnutrition, the measurement of plasma concentration of tryptophan is used as an indicator of appropriate dietary therapy.

**Useful For:** Investigating inadequate tryptophan intake and monitoring dietary treatment

**Interpretation:** If the result is within the respective age-matched reference range, no interpretation is provided. When an abnormal result is reported, an interpretation may be added including a correlation to available clinical information, elements of differential diagnosis, and recommendations for additional biochemical testing, if applicable.

**Reference Values:**
- < or =23 months: 17-75 nmol/mL
- 2 years-17 years: 23-80 nmol/mL
- > or =18 years: 29-77 nmol/mL


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**Tryptophan, Urine**

**Clinical Information:** Amino acids are the basic units that make up proteins and are crucial to virtually all metabolic processes in the body. Tryptophan is an essential amino acid necessary for the synthesis of serotonin, melatonin, and niacin. Hartnup disease is a rare, usually benign, autosomal recessive disorder of renal and intestinal neutral amino acid transport. The clinical features associated with Hartnup disease include an erythematous skin rash on exposed surfaces that is identical to the rash seen in pellagra (niacin deficiency) and cerebral ataxia. Biochemically, it is characterized by increased renal excretion of tryptophan and other neutral amino acids. Newborn screening studies reveal that most affected individuals remain asymptomatic, suggesting that clinical expression of symptoms is dependent on additional genetic or environmental factors (ie, multifactorial disease). Determination of tryptophan by conventional amino acid profiling methods (ninhydrin-based, HPLC) is hampered by coelution with other compounds. This liquid chromatography-tandem mass spectrometry method quantifies tryptophan and is interference free.

**Useful For:** Aids in the screening and monitoring of Hartnup disease

**Interpretation:** If the result is within the respective age-matched reference range, no interpretation is provided. When an abnormal result is reported, an interpretation may be added, including a correlation to available clinical information and recommendations for additional biochemical testing, if applicable.

**Reference Values:**
- < or =35 months: 14-315 nmol/mg creatinine
- 3-8 years: 10-303 nmol/mg creatinine
- 9-17 years: 15-229 nmol/mg creatinine
- > or =18 years: 18-114 nmol/mg creatinine


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**TTF41 (SPT24) + p40 Immunostain, Technical Component Only**

**Clinical Information:** Thyroid transcription factor 1 (TTF1) is a nuclear protein (detected by the chromogen 3,3'-diaminobenzidine: DAB) expressed in thyroid follicular cells, type II pneumocytes, and a subset of bronchial cells. The p40 antibody recognizes the deltaNp63 isoform of p63 (detected by the
chromogen fast red). The predominant localization of p40 is in the basal layer of the stratified squamous and transitional epithelia. Given the relative specificity of TTF1 for cells of thyroid or lung origin, TTF1 is often included in a panel to identify the primary site for carcinomas of unknown origin. The p40 antibody may help to distinguish squamous cell carcinomas from other non-small cell carcinomas.

**Useful For:** Thyroid transcription factor 1 aids in the classification of carcinomas of unknown origin

p40 aids in the classification of carcinomas and lymphomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). If diagnostic consultation by a pathologist is required order PATHC / Pathology Consultation. The positive and negative controls are verified as showing appropriate immunoreactivity. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Reference Values:**
This is not an orderable test. Order PATHC / Pathology Consultation. The consultant will determine the need for special stains.

**Clinical References:**

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**ATTRZ 35352 TTR Gene, Full Gene Analysis**

**Clinical Information:** The systemic amyloidoses are a number of disorders of varying etiology characterized by extracellular protein deposition. The most common form is an acquired amyloidosis secondary to multiple myeloma or monoclonal gammopathy of unknown significance (MGUS) in which the amyloid is composed of immunoglobulin light chains. In addition to light chain amyloidosis, there are a number of acquired amyloidoses caused by the misfolding and precipitation of a wide variety of proteins. There are also hereditary forms of amyloidosis. Due to the clinical overlap between the acquired and hereditary forms, it is imperative to determine the specific type of amyloidosis in order to provide an accurate prognosis and consider appropriate therapeutic interventions. The most common hereditary amyloidosis is familial transthyretin amyloidosis; an autosomal dominant disorder caused by mutations in the transthyretin (TTR) gene. The resulting amino acid substitutions lead to a relatively unstable, amyloidogenic TTR protein. Most individuals begin to exhibit clinical symptoms between the third and seventh decades of life. Typically, TTR-associated amyloidosis is progressive over a course of 5 to 15 years and the most common cause of death is cardiomyopathy. Affected individuals may present with a variety of symptoms, including peripheral neuropathy, blindness, cardiomyopathy, nephropathy, autonomic nervous dysfunction, or bowel dysfunction. More than 90 mutations have now been identified within the TTR gene, which cause TTR-associated familial amyloidosis. Most of the mutations described to date are single base pair changes that result in an amino acid substitution. Some of these mutations correlate with the clinical presentation of amyloidosis. However, several different mutations have been identified which exhibit considerable clinical overlap. It is important to note that this assay does not detect mutations associated with non-TTR forms of familial amyloidosis. Therefore, it is important to first test an affected family member to determine if TTR is involved and to document a specific mutation in the family before testing at risk individuals.

**Useful For:** Diagnosis of adult individuals suspected of having transthyretin-associated familial amyloidosis

**Interpretation:** All detected alterations are evaluated according to American College of Medical
Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.


**RTRP1 113477**

**Tubular Reabsorption of Phosphorus, Random**

Clinical Information: The tubular reabsorption of phosphate (TRP) is the fraction (or percent) of filtered phosphorus that is reabsorbed by renal tubules. Its measurement is useful when evaluating patients with hypophosphatemia. In general, a reduced TRP in the presence of hypophosphatemia is indicative of a renal defect in phosphate reabsorption. The ratio of the maximum rate of tubular phosphate reabsorption to the glomerular filtration rate (TmP/GFR) is considered the most convenient way to evaluate renal phosphate transport and is referred to as the theoretical renal phosphate threshold. This corresponds to the theoretic lower limit of plasma phosphate below which all filtered phosphate would be reabsorbed. Although direct measurements of parathyroid hormone (PTH), which increases renal phosphate excretion have replaced much of the utility of TmP/GFR measurements, it may still be useful in assessing renal reabsorption of phosphorus in a variety of pathological conditions associated with hypophosphatemia.

Useful For: Assessing renal reabsorption of phosphorus in a variety of pathological conditions associated with hypophosphatemia including hypophosphatemic rickets, tumor-induced osteomalacia, and tumoral calcinosis Adjusting phosphate replacement therapy in severe deficiency states monitoring the renal tubular recovery from acquired Fanconi syndrome

Interpretation: Interpretation of tubular reabsorption of phosphate (TRP) and TmP/GFR is dependent upon the clinical situation and should be interpreted in conjunction with the serum phosphorous concentration. TmP/glomerular filtration rate (GFR) is independent of dietary phosphorus intake, tissue release of phosphorus, and GFR.

Reference Values:

**TUBULAR REABSORPTION OF PHOSPHORUS**

>80%

(Although, tubular reabsorption of phosphorus levels must be interpreted in light of the prevailing plasma phosphorus and glomerular filtration rate.)

**TUBULAR MAXIMUM PHOSPHORUS REABSORPTION/GLOMERULAR FILTRATION RATE (TmP/GFR)**

2.6-4.4 mg/dL (0.80-1.35 mmol/L)

**PHOSPHORUS (INORGANIC)**

Males

1-4 years: 4.3-5.4 mg/dL
5-13 years: 3.7-5.4 mg/dL
14-15 years: 3.5-5.3 mg/dL
16-17 years: 3.1-4.7 mg/dL
> or =18 years: 2.5-4.5 mg/dL

Reference values have not been established for patients that are <12 months of age.

Females

1-7 years: 4.3-5.4 mg/dL
PHOSPHORUS, Random Urine
No established reference values

CREATININE Serum
Males(1)
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-14 years: 0.35-0.86 mg/dL
> or =15 years: 0.74-1.35 mg/dL

Females(1)
0-11 months: 0.17-0.42 mg/dL
1-5 years: 0.19-0.49 mg/dL
6-10 years: 0.26-0.61 mg/dL
11-15 years: 0.35-0.86 mg/dL
> or =16 years: 0.59-1.04 mg/dL

CREATININE, Random Urine
No established reference values

**Clinical References:**

**Tumor Necrosis Factor (TNF), Plasma**
**Clinical Information:** Tumor necrosis factor (TNF)-alpha is expressed primarily by activated monocytes as part of the innate immune response to various microbes, gram-negative bacteria in particular.(1) TNF-alpha is synthesized as a type II membrane protein, which can be cleaved by a membrane-associated metalloproteinase. The subunit that is released will polymerize to form a homotrimer, which is the circulating form of TNF-alpha. The primary function of TNF-alpha is to recruit other leukocytes to the site of infection and to stimulate their activation. TNF-alpha also has some systemic effects, including induction of fever through action on the hypothalamus. In cases of severe gram-negative bacterial infection, septic shock can occur. Septic shock is induced by large-scale production of inflammatory cytokines, including TNF-alpha. This disorder is characterized by hypotension, disseminated intravascular coagulation, tachycardia, and increased respiration, and can be fatal. Dysregulation of TNF-alpha expression is thought to be a critical pathogenic mechanism in numerous autoimmune diseases, including inflammatory bowel disease (IBD), rheumatoid arthritis (RA), and ankylosing spondylitis (AS).(2) There are currently 5 monoclonal antibodies approved by the FDA for blockage of TNF-alpha as a clinical treatment.(3,4) The different drugs are approved for various diseases, with some available for treatment of pediatric IBD and juvenile RA.

**Useful For:** Evaluation of patients with suspected systemic infection, in particular infection caused by gram-negative bacteria Evaluation of patients with suspected chronic inflammatory disorders, such as rheumatoid arthritis, inflammatory bowel disease, or ankylosing spondylitis
**Interpretation:** Elevated concentrations of tumor necrosis factor (TNF)-alpha may indicate an ongoing inflammatory response, and could be consistent with a systemic infection, localized infection, or chronic inflammatory disease.

**Reference Values:**
< or = 2.8 pg/mL


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**TUNA 82547**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>Interpretation</th>
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<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

**Turkey Feathers, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


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**Turkey IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be
taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

Turkey, IgE

Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Turmeric (Curcuma longa) IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

Reference Values:

<0.35 kU/L
**Tyrophagus putrescentiae, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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</table>

Reference values apply to all ages.


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**Tyrosinase (TYROS) Immunostain, Technical Component Only**

**Clinical Information:** Tyrosinase is expressed in the majority of melanomas, making it a useful diagnostic marker. This antibody will detect the tyrosinase enzyme in the cytoplasm of normal melanocytes as well as cells of malignant melanoma.

**Useful For:** Aids in the identification of normal melanocytes and malignant melanoma.

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation.
and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**FSABI 58004** Tysabri (Natalizumab) Immunogenicity

**Reference Values:**

Negative

**UBE3Z 35565** UBE3A Gene, Full Gene Analysis

**Clinical Information:** Angelman syndrome (AS) is characterized by significant developmental delay and mental retardation, ataxia, jerky arm movements, unprovoked laughter, seizures, and virtual absence of speech. AS has several known genetic causes. About 65% to 80% of affected individuals have a de novo deletion of essentially the same region of chromosome 15 detected for Prader-Willi syndrome (PWS): 15q11.2-13. The deletion can often be identified by high-resolution chromosome analysis in conjunction with FISH analysis. Molecular testing has shown that the AS deletion occurs only on the copy of chromosome 15 inherited from the mother. In about 5% of patients with AS, the affected individuals have inherited 2 copies of chromosome 15 from their father (paternal uniparental disomy) and no copies of chromosome 15 from their mother. Thus, the individuals with AS resulting from deletion or uniparental disomy are deficient for maternally derived genes from chromosomes 15. Deletions and uniparental disomy occur as de novo events during conception, so the recurrence risk to siblings is very low. Both of these genetic alterations, along with imprinting center defects (accounting for another 2%-5% of AS cases), cause an abnormal methylation pattern in the PWS/AS region of chromosome 15. Another 10% of patients with AS have a documented mutation in the UBE3A gene located in the PW/AS region on chromosome 15. Mutations can either be maternally inherited in an autosomal dominant fashion or de novo. If the mutation is inherited, the risk to all future pregnancies is 50%. If testing of the affected individual's mother confirms she does not carry the mutation, the risk to future pregnancies is low but not zero, as cases of germline mosaicism have been reported. Individuals with a UBE3A mutation will display a normal methylation pattern. No chromosomal or DNA abnormality has been identified in the remainder of clinically diagnosed AS patients (15%-25%). These patients may have genetic alterations that cannot be detected by current testing methods or alterations in as yet unidentified genes. Initial studies to rule-out AS should include high-resolution cytogenetic analysis (CMS / Chromosome Analysis, for Congenital Disorders, Blood) to identify chromosome abnormalities that may have phenotypic overlap with AS, and methylation-sensitive, multiple ligation-dependent probe amplification (PWAS / Prader-Willi/Angelman Syndrome, Molecular Analysis) to identify deletions, duplications, and methylation defects. In cases where methylation analysis is negative, sequencing of the UBE3A gene may provide additional diagnostic information.
Useful For: Confirmation of a diagnosis of Angelman syndrome in patients who have previously tested negative by methylation analysis

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

Ubiquitin (UBIQ) Immunostain, Technical Component Only

Clinical Information: Ubiquitin is a polypeptide of approximately 8.5 kD found in filamentous inclusions and cytosome-related organelles in human idiopathic neurodegenerative diseases, including Alzheimer disease, Pick disease, Lewy body dementia, and Parkinson disease. Ubiquitin is also expressed in Rosenthal fibers in astrocytomas. Ubiquitin protein complexes have also been found in primary lysosome-related granules in mature neutrophils. Ubiquitin labels the periphery of senile plaques and of neurofibrillary tangles in Alzheimer disease, Lewy bodies in Parkinson disease, and Mallory bodies in alcoholic liver disease.

Useful For: Classification of neurodegenerative diseases

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

UDP-Galactose 4' Epimerase (GALE), Blood

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com
Clinical Information: Galactosemia is an autosomal recessive disorder that results from a deficiency of 1 of the 3 enzymes catalyzing the conversion of galactose to glucose: galactose-1-phosphate uridylytransferase (GALT), galactokinase (GALK), and uridine diphosphate galactose-4-epimerase (GALE). Epimerase deficiency galactosemia can be categorized into 3 types: generalized, peripheral, and intermediate. Generalized epimerase deficiency galactosemia results in profoundly decreased enzyme activity in all tissues, whereas peripheral epimerase deficiency galactosemia results in decreased enzyme activity in red and white blood cells, but normal enzyme activity in all other tissues. This is compared to intermediate epimerase deficiency galactosemia which results in decreased enzyme activity in red and white blood cells and less than 50% of normal enzyme levels in other tissues. Clinically, infants with generalized epimerase deficiency galactosemia develop symptoms such as liver and renal dysfunction and mild cataracts when on a normal milk diet, while infants with peripheral or intermediate epimerase deficiency galactosemia do not develop any symptoms. Generalized epimerase deficiency galactosemia is treated by a galactose- and lactose-restricted diet, which can improve or prevent the symptoms of renal and liver dysfunction and mild cataracts. Despite adequate treatment from an early age, individuals with generalized epimerase deficiency galactosemia remain at increased risk for developmental delay and intellectual disability. Unlike patients with classic galactosemia resulting from a GALT deficiency, females with generalized epimerase deficiency galactosemia experience normal puberty and are not at increased risk for premature ovarian failure. Based upon reports by newborn screening programs, the frequency of epimerase deficiency galactosemia in the United States ranges from approximately 1 in 6,700 in African American infants to 1 in 70,000 infants of European ancestry. Galactose-1-phosphate (Gal-1-P) accumulates in the erythrocytes of patients with galactosemia due to either GALT or GALE deficiency. The quantitative measurement of Gal-1-P (GAL1P / Galactose-1-Phosphate (Gal-1-P), Erythrocytes) is useful for monitoring compliance with dietary therapy. Gal-1-P is thought to be the causative factor for development of liver disease in these patients and, because of this, patients should maintain low levels and be monitored on a regular basis. Newborn screening, which identifies potentially affected individuals by measuring total galactose (galactose and Gal-1-P) and/or determining the activity of the GALT enzyme, varies from state to state. The diagnosis of galactosemia is established by follow-up quantitative measurement of GALT enzyme activity. If enzyme levels are normal, but an infant has an elevated Gal-1-P, then epimerase deficiency galactosemia is to be considered. Molecular testing via sequencing of the GALE gene may be performed. See Galactosemia Testing Algorithm in Special Instructions for additional information.

Useful For: Diagnosis of UDP-galactose 4’ epimerase deficiency

Interpretation: An interpretive report will be provided.

Reference Values:
>=3.5 nmol/h/mg of hemoglobin

bilirubin) to its nontoxic, water-soluble form (conjugated bilirubin). Genetic variants in UGT1A1 may cause reduced or absent UGT1A1 enzymatic activity, resulting in conditions associated with unconjugated hyperbilirubinemia including Gilbert syndrome and Crigler-Najjar syndromes types I and II. Gilbert syndrome is the most common hereditary cause of increased bilirubin and is characterized by total serum bilirubin levels of 1 to 6 mg/dL. Gilbert syndrome is generally considered to be an autosomal recessive disorder, although autosomal dominant inheritance has been suggested in some cases. Gilbert syndrome is caused by a 25% to 50% reduction in glucuronidation activity of the UGT1A1 enzyme and is characterized by episodes of mild intermittent jaundice and the absence of liver disease. Crigler-Najjar syndromes types I and II (CN1 and CN2) are autosomal recessive disorders caused by more severe reductions in UGT1A1 glucuronidation activity. CN1 is the most severe form, with complete absence of enzyme activity and total serum bilirubin levels of 20 to 45 mg/dL. Infants with CN1 present with jaundice shortly after birth that persists thereafter. CN2 is milder than CN1, with at least partial UGT1A1 activity and total serum bilirubin ranging from 6 to 20 mg/dL. Phenobarbital, a drug that induces synthesis of a number of hepatic enzymes, is effective in decreasing serum bilirubin levels by approximately 25% in patients with CN2; CN1 does not respond to phenobarbital treatment. If left untreated, the buildup of bilirubin in a newborn can cause bilirubin-induced brain damage, known as kernicterus. In addition to phenobarbital, treatments of CN may include: phototherapy, heme oxygenase inhibitors, oral calcium phosphate and carbonate, and liver transplantation. In addition to the role of UGT1A1 in bilirubin metabolism, this enzyme also plays a role in the metabolism of several drugs. UGT1A1 is involved in the metabolism of irinotecan, a topoisomerase I inhibitor. Irinotecan is a chemotherapy drug used to treat solid tumors including colon, rectal, and lung cancers. It is a prodrug that forms an active metabolite, SN-38. SN-38 is normally inactivated by conjugation with glucuronic acid followed by biliary excretion into the gastrointestinal tract. If UGT1A1 activity is impaired or deficient, SN-38 fails to become conjugated with glucuronic acid, increasing the concentration of SN-38. This can result in severe neutropenia. The combination of neutropenia with diarrhea can be life-threatening. Additional drugs have also been associated with an increased risk for adverse outcomes in patients with reduced UGT1A1 enzyme activity. The FDA drug labels for nilotinib, pazopanib, and belinostat all contain warnings for an increased risk (incidence) of adverse outcomes in patients who have UGT1A1 variants associated with reduced activity. The Clinical Pharmacogenetics Implementation Consortium (CPIC) released guidelines for atazanavir treatment, indicating that patients with homozygous UGT1A1 alleles associated with reduced activity or decreased expression should consider an alternate medication due to a significant risk for developing hyperbilirubinemia (jaundice). The UGT1A1 gene maps to chromosome 2q37 and contains 5 exons. In this assay, the promoter, exons, and exon-intron boundaries are assessed for variants.

**Useful For:**
- Identifying individuals who are at increased risk of adverse drug reactions with drugs that are metabolized by UGT1A1, including irinotecan, atazanavir, nilotinib, pazopanib, and belinostat
- Identifying individuals who are at risk of hyperbilirubinemia
- Follow-up testing for individuals with a suspected UGT1A1 variant, who had negative TA repeat region testing
- Establishing a diagnosis of Gilbert, Crigler-Najjar syndrome type I or type II
- Establishing carrier status for Gilbert, Crigler-Najjar syndrome type I or type II

**Interpretation:** An interpretive report will be provided that includes assessment of risk for UGT1A1-associated adverse drug reactions as well as interpretation for hyperbilirubinemia syndromes. For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables in Special Instructions. This resource includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
UDP-Glucuronosyl Transferase 1A1 TA Repeat Genotype, UGT1A1

**Clinical Information:** Following primary metabolism by the phase I enzymes (by oxidation, reduction, dealkylation, and cleavage in the intestines and liver), many drugs and their metabolites are further modified for excretion by a group of conjugative, phase II enzymes. One of these phase II enzymes, uridine diphosphate (UDP)-glycuronosyl transferase 1A1 (UGT1A1), is responsible for phase II conjugation of certain drugs, like atazanavir, irinotecan, nilotinib, pazopanib, and belinostat. UGT1A1 is additionally responsible for glucuronide conjugation of bilirubin, which renders the bilirubin water soluble and permits excretion of the bilirubin-glucuronide conjugates in urine. Reduced UGT1A gene transcription due to variation in the number of thymine-adenine (TA) repeats in the TATA box of the gene promoter and c.211G->A (*6) results in reduced enzymatic activity and an increased risk for adverse outcomes in response to drugs metabolized by UGT1A1. These variants are also associated with Gilbert syndrome (unconjugated hyperbilirubinemia). The TA repeat number may vary from 5 to 8 TA (TA5-TA8) repeats, with 6 TA (TA6) repeats being the most common allele. TA6 is the reference allele and is considered to have normal UGT1A1 expression. In addition, the rare TA5 repeat (*36: c.-41_-40delTA) has normal UGT1A1 expression. Individuals with TA7 repeat (*28: c.-41_-40dupTA) or the rare TA8 repeat (TA8 or *37: c.-43_-40dupTATA, not distinguished from TA7 with this assay) have decreased expression of UGT1A1. Approximately 10% to 15% of Caucasians and African Americans are homozygous for the TA7 repeat (*28/*28). UGT1A1 is involved in the metabolism of irinotecan, a chemotherapy drug used to treat solid tumors including colon, rectal, and lung cancers. If UGT1A1 activity is reduced or deficient, the active irinotecan metabolite (SN-38) is less efficiently conjugated with glucuronic acid, which leads to an increased concentration of SN-38. This in turn can result in severe neutropenia; and the combination of neutropenia with diarrhea can be life-threatening. Individuals who are homozygous for *28 (TA7) have a 50% higher risk of experiencing severe (grade 4 or 5) neutropenia following the administration of irinotecan. Approximately 40% of individuals treated with irinotecan are heterozygous for the TA7 repeat allele (ie, TA6/TA7 or heterozygous *28). These individuals are also at increased risk of grade 4 neutropenia. The drug label for irinotecan indicates that individuals homozygous or heterozygous for TA repeat variants have a higher risk for severe or life-threatening neutropenia. The risk is thought to be greatest in individuals who receive irinotecan once every 3 weeks. Additional drugs have also been associated with an increased risk for adverse outcomes if the patient has reduced UGT1A1 enzyme activity. The FDA drug labels for atazanavir, nilotinib, pazopanib, and belinostat all contain warnings for an increased risk (incidence) of adverse outcomes in patients who have reduced activity alleles. Recently, the Clinical Pharmacogenetics Implementation Consortium (CPIC) released guidelines for atazanavir treatment that indicate patients who are homozygous for a reduced activity (decreased expression) allele should be considered for an alternate medication due to the significant risk for developing hyperbilirubinemia (jaundice).(2) Gilbert syndrome (GS), found in 5% to 10% of the population, is the most common hereditary cause of increased bilirubin and is associated with usually benign, mild hyperbilirubinemia (bilirubin levels are typically around 3 mg/dL). Gilbert syndrome is caused by a 25% to 50% reduced glucuronidation activity of the UGT1A1 enzyme and characterized by episodes of mild intermittent jaundice and the absence of liver disease. Homozygosity for the reduced activity alleles, UGT1A1*6 (c.211G->A) allele, TA7, and TA8, or compound heterozygosity (*6, TA7, or TA8) is consistent with a diagnosis of Gilbert syndrome. Heterozygosity for *6, TA7 or TA8 is consistent
with carrier status for Gilbert syndrome.

**Useful For:** Identifying individuals who are at increased risk of adverse drug reactions with drugs that are metabolized by UGT1A1; especially irinotecan, nilotinib, pazopanib, and belinostat Identifying individuals with Gilbert syndrome due to the presence of homozygous UGT1A1*6 (c.211G->A) allele, TA7, homozygous TA8, or compound heterozygous *6, TA7 or TA8 Identifying individuals who are carriers of Gilbert syndrome due to the presence of heterozygous TA7 or TA8

**Interpretation:** An interpretive report will be provided. Drug-drug interactions must be considered when predicting the UGT1A1 phenotype, especially in individuals heterozygous for the TA7 polymorphism (see Cautions). For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

**Reference Values:**
An interpretive report will be provided.


**Ulocladium chartarum, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L  Interpretation
Unstable Hemoglobin, Blood

**Clinical Information:** Unstable hemoglobin disease is rare and may be caused by any 1 of a large number of hemoglobin variants. They are inherited as an autosomal dominant trait. The severity of the disease varies according to the hemoglobin variant; there may be no clinical symptoms or the disease may produce a mild, moderate, or severe hemolytic anemia. The stained peripheral blood smear shows anisocytosis, poikilocytosis, basophilic stippling, polychromasia and, sometimes, hypochromia. The reticulocyte count may be increased. Splenomegaly and Heinz bodies may also be present.

**Useful For:** Work-up of congenital hemolytic anemias

**Interpretation:** An abnormal or unstable result is indicative of a hemoglobin variant present. Other confirmatory tests should be performed to identify the hemoglobinopathy (HBELC / Hemoglobin Electrophoresis Cascade, Blood).

**Reference Values:**
Only orderable as part of a profile or as a reflex. For more information see HAEVP / Hemolytic Anemia Evaluation; or HBELC / Hemoglobin Electrophoresis Cascade, Blood; or THEVP / Thalassemia and Hemoglobinopathy Evaluation; or REVE / Erthrocytosis Evaluation; or MEVP / Methemoglobinemia Evaluation.

Normal (reported as normal [stable] or abnormal [unstable])

**Clinical References:**

Uranium, Urine

**Reference Values:**
Reporting limit determined each analysis

Normally: Less than 0.1 mcg/L

Urea, 24 Hour, Urine

**Clinical Information:** Urea is a low molecular weight substance (Mol. Wt.=60) that is freely filtered by glomeruli and the majority is excreted into the urine, although variable amounts are reabsorbed along the nephron. It is the major end product of protein metabolism in humans and other mammals. Approximately 50% of urinary solute excretion and 90% to 95% of total nitrogen excretion is composed of urea under normal conditions. Factors which tend to increase urea excretion include increases in glomerular filtration rate, increased dietary protein intake, protein catabolic conditions, and water diuretic states. Factors which reduce urea excretion include low protein intake and conditions which result in low urine output (eg, dehydration).

**Useful For:** Assessment of protein intake and/or nitrogen balance

**Interpretation:** Because multiple factors (glomerular filtration rate, dietary protein intake, protein catabolic rate, hydration state, etc.) can independently affect the urinary excretion of urea, all of these factors must be taken into account when interpreting the results.
Reference Values:
10-35 g/24 hours


**Urea, Random, Urine**

**Clinical Information:** Urea is a low molecular weight substance (Mol Wt=60) that is freely filtered by glomeruli and the majority is excreted into the urine, although variable amounts are reabsorbed along the nephron. It is the major end product of protein metabolism in humans and other mammals. Approximately 50% of urinary solute excretion and 90% to 95% of total nitrogen excretion is composed of urea under normal conditions. Factors that tend to increase urea excretion include increases in glomerular filtration rate, increased dietary protein intake, protein catabolic conditions, and water diuretic states. Factors that reduce urea excretion include low protein intake and conditions which result in low urine output (eg, dehydration). Urea excretion is a useful marker of protein metabolism. In oliguric patients with a rising creatinine a fractional excretion of urea <35% is consistent with a prerenal cause, while values >35% are more consistent with acute kidney injury.(2) The fractional excretion of sodium is also used for this purpose, but may be more affected by diuretics. Therefore, the fractional excretion of urea may be particularly useful for patients receiving diuretics.

**Useful For:** Assessment of renal failure (prerenal vs acute kidney injury)

**Interpretation:** Fractional excretion of urea <35% is consistent with a prerenal cause.

**Reference Values:**
No established reference values

**Clinical References:**

**Ureaplasma species, Molecular Detection, PCR**

**Clinical Information:** Ureaplasma urealyticum and U parvum have been associated with a number of clinically significant infections, although their clinical significance may not always be clear as they are part of the normal genital flora. U urealyticum and U parvum have been associated with urethritis and epididymitis. They may cause upper urinary tract infection and they have been associated with infected renal stones. U urealyticum and U parvum may be isolated from amniotic fluid of women with preterm labor, premature rupture of membranes, spontaneous term labor, or chorioamnionitis. They may also cause neonatal infections, including meningocencephalitis and pneumonia. In addition, U urealyticum and U parvum have been reported to cause unusual infections, such as prosthetic joint infection and infections in transplant recipients. Recently, U urealyticum and U parvum have been found to cause hyperammonemia in lung transplant recipients.(1) In lung transplant recipients with hyperammonemia, the ideal diagnostic specimen is a lower respiratory specimen (eg, bronchoalveolar lavage fluid), although U urealyticum and U parvum may also be detected in blood. Treatment directed against these organisms has resulted in resolution of hyperammonemia. Culture of Ureaplasma species is laborious, requiring a high degree of technical skill and taking several days. PCR detection is sensitive, specific, and provides same-day results. In addition, PCR allows the differentiation of U urealyticum and U parvum, which is not easily accomplished with culture. PCR assay has replaced conventional culture for U urealyticum and U parvum at Mayo Medical Laboratories due to its speed and equivalent performance to culture.

**Useful For:** Rapid, sensitive, and specific identification of Ureaplasma urealyticum and U parvum from genitourinary, reproductive, bone and joint, and lower respiratory sources

**Interpretation:** A positive PCR result for the presence of a specific sequence found within the Ureaplasma urealyticum and U parvum ureC gene indicates the presence of U urealyticum or U parvum
DNA in the specimen. A negative PCR result indicates the absence of detectable U urealyticum and U parvum DNA in the specimen, but does not rule-out infection as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of U urealyticum or U parvum in quantities less than the limit of detection of the assay.

Reference Values:
Not applicable


Ureaplasma species, Molecular Detection, PCR, Blood

Clinical Information: Ureaplasma urealyticum and U parvum have been associated with a number of clinically significant infections, although their clinical significance may not always be clear as they are part of the normal genital flora. U urealyticum and U parvum have been associated with urethritis and epididymitis. They may cause upper urinary tract infection and they have been associated with infected renal stones. U urealyticum and U parvum may be isolated from amniotic fluid of women with preterm labor, premature rupture of membranes, spontaneous term labor, or chorioamnionitis. They may also cause neonatal infections, including meningitis and pneumonia. In addition, U urealyticum and U parvum have been reported to cause unusual infections, such as prosthetic joint infection and infections in transplant recipients. Recently, U urealyticum and U parvum have been found to cause hyperammonemia in lung transplant recipients.(1) In lung transplant recipients with hyperammonemia, the ideal diagnostic specimen is a lower respiratory specimen (eg, bronchoalveolar lavage fluid), although U urealyticum and U parvum may also be detected in blood. Treatment directed against these organisms has resulted in resolution of hyperammonemia. Culture of Ureaplasma species is laborious, requiring a high degree of technical skill and taking several days. PCR detection is sensitive, specific, and provides same-day results. In addition, PCR allows the differentiation of U urealyticum and U parvum, which is not easily accomplished with culture. PCR assay has replaced conventional culture for U urealyticum and U parvum at Mayo Medical Laboratories due to its speed and equivalent performance to culture.

Useful For: Rapid, sensitive, and specific identification of Ureaplasma urealyticum and U parvum from whole blood

Interpretation: A positive PCR result for the presence of a specific sequence found within the Ureaplasma urealyticum and U parvum ureC gene indicates the presence of U urealyticum or U parvum DNA in the specimen. A negative PCR result indicates the absence of detectable U urealyticum and U parvum DNA in the specimen, but does not rule-out infection as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of U urealyticum or U parvum in quantities less than the limit of detection of the assay.

Reference Values:
Not applicable

Ureaplasma species, Molecular Detection, PCR, Plasma

Clinical Information: Ureaplasma urealyticum and U parvum have been associated with a number of clinically significant infections, although their clinical significance may not always be clear as they are part of the normal genital flora. U urealyticum and U parvum have been associated with urethritis and epididymitis. They may cause upper urinary tract infection and they have been associated with infected renal stones. U urealyticum and U parvum may be isolated from amniotic fluid of women with preterm labor, premature rupture of membranes, spontaneous term labor, or chorioamnionitis. They may also cause neonatal infections, including meningococcal and pneumonia. In addition, U urealyticum and U parvum have been reported to cause unusual infections, such as prosthetic joint infection and infections in transplant recipients. Recently, U urealyticum and U parvum have been found to cause hyperammonemia in lung transplant recipients. In lung transplant recipients with hyperammonemia, the ideal diagnostic specimen is a lower respiratory specimen (e.g., bronchoalveolar lavage fluid), although U urealyticum and U parvum may also be detected in blood. Treatment directed against these organisms has resulted in resolution of hyperammonemia. Culture of Ureaplasma species is laborious, requiring a high degree of technical skill and taking several days. PCR detection is sensitive, specific, and provides same-day results. In addition, PCR allows the differentiation of U urealyticum and U parvum, which is not easily accomplished with culture. PCR assay has replaced conventional culture for U urealyticum and U parvum at Mayo Medical Laboratories due to its speed and equivalent performance to culture.

Useful For: Rapid, sensitive, and specific identification of Ureaplasma urealyticum and U parvum from plasma

Interpretation: A positive PCR result for the presence of a specific sequence found within the Ureaplasma urealyticum and U parvum ureC gene indicates the presence of U urealyticum or U parvum DNA in the specimen. A negative PCR result indicates the absence of detectable U urealyticum and U parvum DNA in the specimen, but does not rule-out infection as false-negative results may occur due to inhibition of PCR, sequence variability underlying the primers and probes, or the presence of U urealyticum or U parvum in quantities below the limit of detection of the assay.

Reference Values: Not applicable


Uric Acid, 24 Hour, Urine

Clinical Information: Uric acid is the end-product of purine metabolism. It is freely filtered by the glomeruli and most is reabsorbed by the tubules. There is also active tubular secretion. Increased levels of uric acid in the urine usually accompany increased plasma uric acid levels unless there is a decreased excretion of uric acid by the kidneys. Urine uric acid levels reflect the amount of dietary purines and also
endogenous nucleic acid breakdown.

**Useful For:** Assessment and management of patients with kidney stones, particularly uric acid stones

**Interpretation:** Urinary uric acid excretion is elevated in a significant proportion of patients with uric acid stones. Uric acid excretion can be either decreased or increased in response to a variety of pharmacologic agents. Urine uric acid levels are elevated in states of uric acid overproduction such as in leukemia and polycythemia and after intake of food rich in nucleoproteins.

**Reference Values:**

> or = 16 years: Diet-dependent: <750 mg/24 hours

Reference values have not been established for patients who are less than 16 years of age.

The reference value is for a 24-hour collection. Specimens collected for other than a 24-hour time period are reported in unit of mg/dL for which reference values are not established.


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**FUABF**

Uric Acid, Body Fluid

**Reference Values:**

Units: mg/dL

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**RURCU**

Uric Acid, Random, Urine

**Clinical Information:** Uric acid is the end-product of purine metabolism. It is freely filtered by the glomeruli and most is reabsorbed by the tubules. There is also active tubular secretion. Increased levels of uric acid in the urine usually accompany increased plasma uric acid levels unless there is a decreased excretion of uric acid by the kidneys. Urine uric acid levels reflect the amount of dietary purines and also endogenous nucleic acid breakdown. Acute uric acid nephropathy can cause acute renal failure due to uric acid precipitation within tubules. This is most commonly seen in patients with hematologic malignancies (eg, lymphoma, leukemia), often after acute lysis of cells by chemotherapy. Less commonly this may be seen with seizures, treatment of solid tumors, overproduction of uric acid in metabolic disorders such as Lesch-Nyhan syndrome or decreased uric acid reabsorption in the proximal nephron due to tubular disorder (Fanconi syndrome).

**Useful For:** Differentiation of acute uric acid nephropathy from other causes of acute renal failure

Patients who cannot collect a 24-hour specimen, typically small children, a uric acid to creatinine ratio can be used to approximate 24-hour excretion

**Interpretation:** Uric acid excretion can be either decreased or increased in response to a variety of pharmacologic agents. Urine uric acid levels are elevated in states of uric acid overproduction such as in leukemia and polycythemia and after intake of food rich in nucleoproteins. A uric acid to creatinine ratio (mg/mg) >1.0 is consistent with acute uric acid nephropathy, whereas values <0.75 are consistent with other causes of acute renal failure.(1) A timed 24-hour collection is usually the preferred method for measuring and interpreting this urinary analyte. Random collections normalized to urinary creatinine may be of clinical use in 2 scenarios, however: -When acute renal failure secondary to uric acid is suspected, a uric acid to creatinine ratio (mg/mg) >1.0 is consistent with acute uric acid nephropathy, whereas values <0.75 are consistent with other causes of acute renal failure.(1) -In patients who cannot collect a 24-hour specimen, typically small children, a uric acid creatinine ratio can be used to approximate 24-hour excretion. Pediatric Reference Ranges of Uric Acid/Creatinine (mg/mg)(2) Age (year) 5th Percentile 95th Percentile 0-0.5 >1.189 <2.378 0.5-1 >1.040 <2.229 1-2 >0.743 <2.080 2-3 >0.698 <1.932 3.5 >0.594 <1.635 5-7 >0.446 <1.189 7-10 >0.386 <0.832 10-14 >0.297 <0.654 14-17 >0.297 <0.594

**Reference Values:**

No established reference values

**Uric Acid, Serum**

**Clinical Information:** Uric acid is the final product of purine metabolism in humans. Purines, compounds that are vital components of nucleic acids and coenzymes, may be synthesized in the body or they may be obtained by ingesting foods rich in nucleic material (eg, liver, sweetbreads). Approximately 75% of the uric acid excreted is lost in the urine; most of the remainder is secreted into the gastrointestinal tract where it is degraded to allantoin and other compounds by bacterial enzymes. Asymptomatic hyperuricemia is frequently detected through biochemical screening. The major causes of hyperuricemia are increased purine synthesis, inherited metabolic disorder, excess dietary purine intake, increased nucleic acid turnover, malignancy, cytotoxic drugs, and decreased excretion due to chronic renal failure or increased renal reabsorption. Long-term follow-up of these patients is undertaken because many are at risk of developing renal disease; few of these patients ever develop the clinical syndrome of gout. Hypouricemia, often defined as serum urate below 2.0 mg/dL, is much less common than hyperuricemia. It may be secondary to severe hepatocellular disease with reduced purine synthesis, defective renal tubular reabsorption, overtreatment of hyperuricemia with allopurinol, as well as some cancer therapies (eg, 6-mercaptopurine).

**Useful For:** Diagnosis and treatment of renal failure Monitoring patients receiving cytotoxic drugs and a variety of other disorders, including gout, leukemia, psoriasis, starvation and other wasting conditions

**Interpretation:** Hyperuricemia is most commonly defined by serum or plasma uric acid concentrations above 8.0 mg/dL in males or above 6.1 mg/dL in females.

**Reference Values:**

**Males**
- 1-10 years: 2.4-5.4 mg/dL
- 11 years: 2.7-5.9 mg/dL
- 12 years: 3.1-6.4 mg/dL
- 13 years: 3.4-6.9 mg/dL
- 14 years: 3.7-7.4 mg/dL
- 15 years: 4.0-7.8 mg/dL
- > or =16 years: 3.7-8.0 mg/dL

Reference values have not been established for patients who are <12 months of age.

**Females**
- 1 year: 2.1-4.9 mg/dL
- 2 years: 2.1-5.0 mg/dL
- 3 years: 2.2-5.1 mg/dL
- 4 years: 2.3-5.2 mg/dL
- 5 years: 2.3-5.3 mg/dL
- 6 years: 2.3-5.4 mg/dL
- 7-8 years: 2.3-5.5 mg/dL
- 9-10 years: 2.3-5.7 mg/dL
- 11 years: 2.3-5.8 mg/dL
- 12 years: 2.3-5.9 mg/dL
- > or =13 years: 2.7-6.1 mg/dL

Reference values have not been established for patients who are <12 months of age.

Urinalysis, Complete, Includes Microscopic

Clinical Information: The kidney plays a key role in the excretion of by-products of cellular metabolism and regulation of water, acid-base, and electrolyte balance. Urine is produced by filtration of plasma in the renal glomeruli, followed by tubular secretion and reabsorption of water and other compounds. Abnormalities detected by urinalysis may reflect either urinary tract diseases (eg, infection, glomerulonephritis, loss of concentrating capacity) or extrarenal disease processes (eg, glucosuria in diabetes, proteinuria in monoclonal gammopathies, bilirubinuria in liver disease).

Useful For: Screening for urinary tract diseases and some nonrenal diseases

Interpretation: Microscopy: RBCs, WBCs, renal tubular epithelial (RTE) cells, transitional epithelial cells, squamous epithelial cells, casts, sperm, free fat, oval fat bodies, bacteria, and pathologic crystals are reported. RBC casts are almost always indicative of glomerulonephritis. White cell casts are typically an indication of acute interstitial nephritis or pyelonephritis, but can also be seen in glomerulonephritides because there is often a component of accompanying interstitial nephritis. Fatty casts and free fat are often seen in patients with nephrotic syndrome or other glomerular diseases associated with significant proteinuria. Granular casts are observed in a number of disorders and are thought to be formed from partially degraded cellular casts, or are protein-derived casts. Hyaline casts are not thought to be indicative of any disease process, but increased numbers may be seen in concentrated urine specimens. Waxy casts and broad casts are most often observed in advanced renal failure. Increased numbers of RTE cells are indicators of renal tubular injury. Increased numbers of RTE may be caused by drugs with renal tubular toxicity (eg, cyclosporine A, aminoglycosides, cisplatin, radio-contrast media, acetaminophen overdose), interstitial nephritis, hypotension (surgical, sepsis, obstetric complications), or heme pigments from hemoglobinuria or myoglobinuria from rhabdomyolysis (eg, alcoholism, heat stroke, seizures, sickle cell trait). Newborns often shed RTE cells in their urine. The presence of squamous cells suggests that the specimen may not have been an optimal clean-catch specimen and could be contaminated with skin flora. Recommendations by an American Urological Association panel, based upon careful review of all available published outcome studies that contained results of detailed hematuria workups within actual patient populations, are that patients with more than 3 RBCs per high-power field in 2 out of 3 properly collected urine specimens should be considered to have microhematuria and, hence, evaluated for possible pathologic causes. However, the panel also noted that there is no absolute lower limit for hematuria, and risk factors for significant disease should be taken into consideration before deciding to defer an evaluation in patients with only 1 or 2 RBCs per high-power field. High-risk patients, especially those with a history of smoking or chemical exposure, should still be considered for a full urologic evaluation even after a properly performed urinalysis documented the presence of at least 3 RBCs per high-power field. In certain patients, even 1 or 2 RBCs per high-powered field might merit evaluation.(1) Osmolality: Osmolality is an index of the solute concentration of osmotically active particles, principally sodium, chloride, potassium, and urea; glucose can contribute significantly to the osmolality when present in substantial amounts. The ability of the kidney to maintain both tonicity and water balance of the extracellular fluid can be evaluated by measuring the osmolality of the urine. More information concerning the state of renal water handling or abnormalities of urine dilution or concentration can be obtained if urinary osmolality is compared to serum osmolality. Normally, the ratio of urine osmolality to serum osmolality is 1.0 to 3.0, reflecting a wide range of urine osmolality. In a random urine specimen, a protein/creatinine or protein/osmolality ratio can be used to roughly approximate 24-hour excretion rates. The normal protein-to-creatinine ratio for adult males is less than 0.11 mg/mg creatinine and for adult females is less than 0.16 mg/mg creatinine. The normal protein-to-osmolality ratio for adults is less than 0.42.(1) For patients under 18 years of age no reference range has been established. Reference values for osmolality: -0-12 months: 50-750 mOsm/kg ->12 months: 150-1,150 mOsm/kg -Please note above the age of 20 there is an age-dependent decline in the upper reference range of approximately 5 mOsm/kg/year. Protein: This test detects the presence of overt proteinuria (>300 mg/day). However, normal urinary protein excretion is less than 30 mg/day. The presence of microalbuminuria (30-300 mg/day) is not detected by this method. Overt proteinuria is seen in both renal (eg, glomerulonephritis, renal tubular diseases, pyelonephritis) and nonrenal diseases (eg, myeloma, congestive heart failure, dehydration). Reference values for protein: <26 mg/dL. Reference values have not been established for patients under 18 years of age. Glucose: The test is specific for glucose. No other substance excreted in
urine is known to give a positive result, including other reducing substances (e.g., galactose, fructose, and lactose). This test may be used to determine whether the reducing substance found in urine is glucose. Glucosuria occurs when the renal threshold for glucose is exceeded (typically >180 mg/dL); this is most commonly, although not exclusively, seen in diabetes. Reference values for glucose: <16 mg/dL pH: Urine pH is affected by diet, medications, systemic acid-base disturbances, and renal tubular function. pH may affect urinary stone formation. For example, urine pH below 6.0 may help reduce the tendency for calcium phosphate stones and pH greater than 6.0 may reduce the tendency for uric acid stone formation. Ketones: Produced during metabolism of fat, increased ketones may occur during physiological stress conditions such as fasting, pregnancy, strenuous exercise, and frequent vomiting. In diabetics who are unable to efficiently utilize glucose due to a lack of insulin, starvation, or with other abnormalities of carbohydrate or lipid metabolism, ketones may appear in the urine in large amounts before serum ketone is elevated. Bilirubin: Bilirubinuria is an indicator of liver disease and biliary tract obstruction. Hemoglobin: Hemoglobinuria is an indicator of intravascular hemolysis. The test is equally sensitive to myoglobin as to hemoglobin. The presence of hemoglobin, in the absence of RBCs, is consistent with intravascular hemolysis. RBCs may be missed if lysis occurred prior to analysis; the absence of RBCs should be confirmed by examining a fresh specimen. The presence of myoglobin may be confirmed by MYGLU / Myoglobin, Urine.

Reference Values:
Descriptive report

Clinical References:

Uroporphyrinogen Decarboxylase (UPG D), Washed Erythrocytes

Clinical Information: The porphyrias are a group of inherited disorders resulting from enzyme defects in the heme biosynthetic pathway. Porphyria cutanea tarda (PCT) is the most common porphyria resulting from a partial deficiency of hepatocyte and/or erythrocyte uroporphyrinogen decarboxylase (UROD). PCT is classified into 3 subtypes. The most frequently encountered is type I, a sporadic or acquired form, typically associated with concomitant disease or other precipitating factors. Patients exhibit normal UROD activity in erythrocytes but decreased hepatic activity. This differs from type II PCT in which patients exhibit approximately 50% activity in both erythrocytes and hepatocytes. Type II accounts for about 20% of cases and is inherited in an autosomal dominant manner with low penetrance. Type III is a rare familial form seen in less than 5% of PCT cases. As in type I, patients with type III PCT have normal UROD activity in erythrocytes with decreased hepatic activity. Type III cases are distinguished from type I by the history of other affected family members. Hepatoerythropoietic porphyria (HEP) is a rare autosomal recessive form of porphyria that typically presents in early childhood. Patients
have a severe deficiency of UROD, with activity levels 10% of normal in both hepatocytes and erythrocytes. All forms of PCT and HEP result in accumulation of uroporphyrin and intermediary carboxyl porphyrins in skin, subcutaneous tissues, and the liver. The most prominent clinical characteristics are cutaneous photosensitivity and scarring on sun-exposed surfaces. Patients experience chronic blistering lesions resulting from mild trauma to sun-exposed areas. These fluid-filled vesicles rupture easily, become crusted, and heal slowly. Secondary infections can cause areas of hypo- or hyperpigmentation or sclerodermatous changes and may result in the development of alopecia at sites of repeated skin damage. Liver disease is common in patients with PCT as evidenced by abnormal liver function tests and with 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Cutaneous) Testing Algorithm in Special Instructions or call 800-533-1710 to discuss testing strategies.

Useful For: Diagnosis of porphyria cutanea tarda type II and hepatoerythropoietic porphyria

Interpretation: Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach one of the laboratory directors in case the referring physician has additional questions.

Reference Values:
>1.0 Relative Units (normal)
0.80-0.99 Relative Units (indeterminate)
<0.80 Relative Units (porphyria cutanea tarda or hepatoerythropoietic porphyria)

damage. Liver disease is common in patients with PCT as evidenced by abnormal liver function tests and with 30% to 40% of patients developing cirrhosis. In addition, there is an increased risk of hepatocellular carcinoma. The workup of patients with a suspected porphyria is most effective when following a stepwise approach. See Porphyria (Cutaneous) Testing Algorithm in Special Instructions or call 800-533-17140 to discuss testing strategies.

**Useful For:** Preferred test for the confirmation of a diagnosis of porphyria cutanea tarda type II and hepatocerebroplastic porphyria

**Interpretation:** Abnormal results are reported with a detailed interpretation that may include an overview of the results and their significance, a correlation to available clinical information provided with the specimen, differential diagnosis, recommendations for additional testing when indicated and available, and a phone number to reach a laboratory director in case the referring physician has additional questions.

**Reference Values:**
> 1.0 Relative Units (normal)
0.80-0.99 Relative Units (indeterminate)
<0.80 Relative Units (porphyria cutanea tarda or hepatocerebroplastic porphyria)

**Clinical References:**

UroVysion for Detection of Bladder Cancer, Urine

**Clinical Information:** Cystoscopy and urine cytology have been the primary methods for detecting urothelial carcinoma (UC). Unfortunately urine cytology has relatively poor sensitivity for the detection of recurrent UC. This is problematic because patients who have undetected recurrent tumors may have tumor progression that places them at increased risk of developing metastatic UC. The UroVysion assay is a FISH assay for the detection of recurrent UC. The UroVysion probe set contains probes to the centromeres of chromosomes 3, 7, and 17, and a locus-specific probe to the 9p21 band (site of the P16 tumor suppressor gene). The UroVysion assay detects cells with chromosomal abnormalities that are consistent with a diagnosis of UC. Studies have shown that the assay has higher sensitivity than urine cytology but similar specificity for the detection of recurrent UC. The UroVysion assay also demonstrates higher specificity than the BTA-stat assay for recurrent UC.

**Useful For:** Monitoring for tumor recurrence in patients with a history of urothelial carcinoma involving the bladder or upper urinary tract. Assessing patients with hematuria for urothelial carcinoma.

**Interpretation:** Lower Tract Samples Abnormal: any specimen satisfying 1 of the following criteria:
- Four or more cells with gains of 2 or more chromosomes
- Ten or more cells with a gain of a single chromosome or 10 or more cells with tetrasomic signal patterns (ie, 4 copies for each of the 4 probes)
- Homozygous deletion of the 9p21 locus in > or =20% of the cells analyzed For cases that are abnormal, the percentage of abnormal cells and type of chromosomal abnormality (ie, polysomy, trisomy, tetrasomy, or homozygous 9p21 deletion) are indicated in the test report. Negative: Fewer than 4 cells with gains of 2 or more chromosomes -Fewer than 10 cells with gain of a single chromosome or tetrasomy -Less than 20% of cells with homozygous 9p21 deletion

Upper Tract Samples Abnormal: any upper tract specimen satisfying 1 of the following criteria:
- Four or more hypertetrasomy cells with at least 5 copies of 2 or more chromosomes
- Ten or more cells with a gain of a single chromosome or > or =10% or more cells with tetrasomic or near-tetrasomic signal patterns (ie, 4 copies for each of the 4 probes)
- Homozygous deletion of the 9p21 locus in > or =20% of the cells analyzed Negative: Fewer than 4 cells with hypertetrasomy with at least 5 copies of 2 or more chromosomes -Fewer than 10% with tetrasomy -Less than 20% of cells with homozygous 9p21 deletion

**Reference Values:**
An interpretive report will be provided.

bone, osteosarcoma, osteoblastoma, brown tumor, cherubism, and vascular neoplasms. Nodular fasciitis (NF) is a self-limited mesenchymal lesion of myofibroblastic differentiation. NF’s rapid growth, rich cellularity, and brisk mitotic activity may lead to a misdiagnosis of sarcoma. USP6 rearrangements are detectable in 90% of NF but not in other conditions that may simulate NF, including dermatofibroma, cellular fibrous histiocytoma, fibromatosis, and a large variety of sarcomas.

**Useful For:** Supporting the diagnosis of aneurysmal bone cyst or nodular fasciitis

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for the USP6 FISH probe (positive result). A positive result is consistent with rearrangement of the USP6 gene locus on 17p13 and supports the diagnosis of aneurysmal bone cyst (ABC) or nodular fasciitis (NF). A negative result is consistent with no rearrangement of the USP6 gene locus on 17p13. However, this result does not exclude the diagnosis of ABC or NF. Rearrangement varies in individual tumors and among different cells in the same tumor.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**
3. Fletcher CDM, Unni KK, Mertens F: World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Soft Tissue and Bone. IARC Press, Lyon, France, 2005, pp 48-49

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**Ustekinumab and Anti-Ustekinumab Antibodies, Serum**

**Interpretation:** Ustekinumab (UST) -The maintenance study showed that both UST 90 mg IM q8w and q12w maintained clinical response and remission through Week 44. However, the q8w regimen more consistently demonstrated efficacy across the range of endpoints.1 -In a sub study of patients (n=102) with endoscopy at baseline and Week 44, the proportions of patients achieving endoscopic response, endoscopic remission, and mucosal healing were higher in the 2nd (> 0.5 ug/ml - 1.39 ug/ml), 3rd (>1.39 ug/ml - 2.67 ug/ml), and 4th (>2.67 ug/ml) concentration quartiles.2 -A second study of patients with CD treated with UST showed 78% of patients were receiving UST 90 mg IM every 4 weeks after > 6 months.3 Antibodies to Ustekinumab -In the phase II clinical trial, the incidence of antibodies to UST was 0.7% at week 36.2 In the pooled results of the phase III clinical trial, the incidence of antibodies to UST was 2.3% through one year.1 -Some patients on biologic therapy may develop antibodies that resolve over time. 7,8,9

**Reference Values:**
Clinically Reportable Ranges:
- Ustekinumab 0.1 - 10 ug/mL
- Anti-Ustekinumab antibody 5 - 100 AU/mL

**Clinical References:**

**Ustilago nuda, Mold Grain Rust, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

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<th>Class</th>
<th>Interpretation</th>
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**Uveal Melanoma, Chromosome 3 Monosomy, FISH, Tissue**

**Clinical Information:** Uveal melanoma is the most common type of primary intraocular...
malignancy in adults, with an annual incidence of 6 per million. These melanomas arise within pigmented cells of the uveal tract of the eye, which consists of the choroid, ciliary body, and iris. Overall, mortality rates in patients with uveal melanoma are quite high (approximately 50%) and are due to metastatic disease. Identifying patients likely to develop metastasis is critical for establishing patient prognosis. Previous studies have demonstrated that monosomy 3 is highly correlated with the development of metastatic disease in patients with uveal melanoma.

**Useful For:** As an aid to prognosis in patients with uveal melanoma when used in conjunction with an anatomic pathology consultation

**Interpretation:** A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for chromosome 3 probe set. A positive result is consistent with monosomy 3 and a higher risk for metastatic disease in uveal melanoma patients. A negative result suggests that aneuploidy of chromosome 3 is not present.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FNSVG 75140 Vaginitis (VG), NuSwab**

**Clinical Information:** This test is intended to be used as an aid to the diagnosis of bacterial vaginosis (BV) in women with a clinical presentation consistent with this disorder. The BV test utilizes semiquantitative PCR analysis of the three most predictive marker organisms (Atopobium vaginae, BVAB-2, and Megasphaera-1) to generate a total score that correlates directly with the presence or absence of BV. In this test system, samples with a score of 0 to 1 are considered negative for BV, samples with a score of 3 to 6 are positive for BV, and samples with a score of 2 are indeterminate for BV.

**Useful For:** Used to detect the presence of Candida albicans and Candida glabrata DNA in vaginal samples as an aid to the diagnosis of vulvovaginal candidiasis in symptomatic women. Also used in the diagnosis of Trichomonas vaginalis infections.

**Reference Values:**
- Candida albicans, NAA: Negative
- Candida glabrata, NAA: Negative
- Trich vag by NAA: Negative

**VALPG 37067 Valproic Acid, Free and Total, Serum**

**Clinical Information:** Valproic acid (valproate, Depakote, or Depakene) is an effective medication for absence seizures, generalized tonic-clonic seizures, and partial seizures, when administered alone or in conjunction with other antiepileptic agents. The valproic acid that circulates in blood is 85% to 90% protein-bound under normal circumstances. In uremia or during concomitant therapy with other drugs that are highly protein-bound (such as phenytoin), valproic acid is displaced from protein, resulting in a higher free fraction of the drug circulating in blood. Since neurologic activity and toxicity of valproic acid are directly related to the unbound fraction of drug, adjustment of dosage based on knowledge of the free
valproic acid concentration may be useful in the following situations: concomitant use of highly protein-bound drugs (usually >80% bound), hypoalbuminemia, pregnancy, renal or hepatic failure, and in the elderly. In these situations, the total valproic acid concentration in the blood may underestimate the disproportionately higher free valproic acid fraction.

**Useful For:** Monitoring both total and free valproic acid levels in therapy Assessing compliance Evaluating potential toxicity

**Interpretation:** The generally acceptable range for total valproic acid used as a reference to guide its therapy is 50 to 125 mcg/mL. The corresponding range of free valproic acid concentration for clinical reference is 5 to 25 mcg/mL. Low free valproic acid concentration relative to these ranges may suggest inadequate dosing, while a high free valproic acid concentration may be associated with toxic effects. Because the concentration of valproic acid fluctuates considerably depending on the time from last dose, interpretation of the clinical significance of the valproic acid concentration must take into consideration the timing of the blood specimen. For this reason, 2 collections are sometimes made to assess the trough and peak concentrations.

**Reference Values:**

**VALPROIC ACID, TOTAL**
- Therapeutic: 50 (trough)-125 (peak) mcg/mL
- Critical value: > or =151 mcg/mL

**VALPROIC ACID, FREE**
- Therapeutic: 5-25 mcg/mL
- Critical value: >30 mcg/mL

**Clinical References:**
last dose, interpretation of the clinical significance of the valproic acid concentration must take into consideration the timing of the blood specimen. For this reason, 2 collections are sometimes made to assess the trough and peak concentrations.

**Reference Values:**
Therapeutic: 5-25 mcg/mL
Critical value: >30 mcg/mL

**Clinical References:**

**Valproic Acid, Total, Serum**

**Clinical Information:** Valproic acid (valproate, Depakote, or Depakene) is used for treatment of simple and complex absence seizures and as combination therapy with other anticonvulsants for control of generalized seizures that include absence seizures. Valproic acid is initially dosed at 15 mg/kg/day, with dosage increases over time to a maximum of 60 mg/kg/day. The volume of distribution of valproic acid is 0.2 L/kg and its half-life is 10 to 14 hours in adults, and shorter in children. It is approximately 90% protein bound. Hepatic failure and a Reyes-like syndrome associated with administration of valproic acid at therapeutic levels have been reported. Careful monitoring of liver function during the first 6 months of therapy is required. Major side effects such as central nervous system depression, thrombocytopenia, and hepatic dysfunction are likely to be experienced if the peak level regularly is above 125 mcg/mL. Analysis of free valproic acid levels may be useful in delineating the cause of toxicity when the total concentration is not excessive. Valproic acid exhibits substantial effects on the pharmacology of phenytoin, whereas phenytoin exhibits only a limited effect on valproic acid. This is due to the relative abundance of the 2 drugs in the body. Valproic acid is present at a 2- to 3-fold mass excess and a 5- to 7-fold molar excess.

**Useful For:** Monitoring total valproic acid in therapy Assessing compliance Evaluating potential toxicity

**Interpretation:** Optimal response is usually observed when the trough level is above 50 mcg/mL. Peak levels should not exceed 125 mcg/mL.

**Reference Values:**
Therapeutic: 50 (trough)-125 (peak) mcg/mL
Critical value: > or =151 mcg/mL

**Clinical References:**

**Vanadium, Serum**

**Clinical Information:** The element vanadium, naturally found in minerals and rocks, is considered an essential element for mammals, although conclusive evidence for humans is lacking. Animal studies have shown that vanadium is essential for mammalian growth and reproduction, iron and lipid metabolism, and RBC production. Vanadium is recovered from minerals or as a by-product of iron, titanium, and uranium refining. Vanadium pentoxide is used in the production of special steels. Vanadium compounds are used as catalysts for polypropylene production and synthesis of inorganic and organic chemicals. Vanadium compounds are used in dyes, photography, ceramics, and in the production of special glasses. Vanadium also is a component of a fiber mesh prosthetic alloy. The main source of vanadium intake for the general
population is food, with an estimated daily intake of 20 mcg, of which most is excreted in the feces, without absorption. Absorption through the inhalation route results in more effective uptake. About 90% of blood vanadium is found in serum. The half-life in serum is not well documented, but it appears to be on the order of several days. Although there is minimal evidence for the nature of vanadium complexation in the body, research suggests transferrin will bind available ionized vanadium. Currently, there is no clinical data to support the need for taking vanadium supplements such as vanadyl sulfate, vanadium colloid, or any other form. This test provides no information regarding any theoretical vanadium deficiency. Vanadium has been recognized as an occupational hazard for >20 years. Elevated atmospheric vanadium levels can result from burning fossil fuels with a high vanadium content. Inhalation and ingestion are the primary exposure routes. Vanadium exposure can result in a metallic taste and so-called “green tongue.” Sensitization can result in asthma or eczema. Vanadium intoxication is effectively treated with ascorbic acid. Increased vanadium serum concentrations are observed in dialysis patients and those with compromised renal function since the kidney is primarily responsible for vanadium elimination. Elevated serum vanadium levels have been observed in patients with joint replacements; concentrations are likely to be increased above the reference range in patients with metallic joint prosthesis. Prosthetic devices produced by Zimmer Company and Johnson and Johnson typically are made of aluminum, vanadium, and titanium. Prosthetic devices produced by Depuy Company, Dow Corning, Howmedica, LCS, PCA, Osteonics, Richards Company, Tricon, and Whiteside typically are made of chromium, cobalt, and molybdenum. This list of products is incomplete, and these products change occasionally; see prosthesis product information for each device for composition details.

**Useful For:** Detecting vanadium toxicity Monitoring metallic prosthetic implant wear

**Interpretation:** Values <1.0 ng/mL are normal. Values >5.0 ng/mL indicate probable exposure. Prosthesis wear is known to result in increased circulating concentration of metal ions. (2-3) Modest increase (1-2 ng/mL) in serum vanadium concentration is likely to be associated with a prosthetic device in good condition. Serum concentrations >5 ng/mL in a patient with a vanadium-based implant suggest significant prosthesis wear. Increased serum trace element concentrations in the absence of corroborating clinical information do not independently predict prosthesis wear or failure.

**Reference Values:**
Normal: <1.0 ng/mL

**Clinical References:**

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**Vancomycin, Peak, Serum**

**Clinical Information:** Vancomycin is an antibiotic used to treat infections caused by gram-positive organisms that are resistant to beta-lactam antibiotics, such as methicillin-resistant staphylococci (MRSA), Streptococcus viridans group, penicillin/cephalosporin-resistant S pneumoniae, and penicillin/ampicillin-resistant Enterococcus species. The oral formulation, which is not absorbed, is used in the treatment of pseudomembranous colitis caused by Clostridium difficile. Vancomycin is also used when patients are intolerant or allergic to beta lactams. Vancomycin has been associated with nephrotoxicity and ototoxicity, although it appears that many of these reports reflected impurities in early formulations. Monitoring of vancomycin-related nephrotoxicity is recommended only for patients with reduced renal function, those receiving aggressive or prolonged vancomycin regimens, or those at high risk including patients comededicated with other nephrotoxic agents. Trough concentrations are recommended for therapeutic monitoring of vancomycin, preferably acquired at steady-state (just before fourth dose). To avoid development of resistance, vancomycin trough levels should remain above 10.0 mcg/mL. Complicated infections require higher target levels, typically 15.0 to 20.0 mcg/mL. Peak concentrations do not correlate well to efficacy or nephrotoxicity, but may be useful for pharmacokinetic analyses (eg, area under the curve: AUC studies) or for select patients.

**Useful For:** Monitoring peak levels in selected patients receiving vancomycin therapy
Interpretation: Typical peak levels are between 20.0 and 45.0 mcg/mL. Peak levels are not recommended for monitoring, except in select circumstances such as when performing pharmacokinetic analyses (eg, area under the curve: AUC determination). These levels are consistent with Mayo Clinic Antimicrobial Therapy Guidelines.

Reference Values:
Therapeutic: 20.0-45.0 mcg/mL

**Clinical Information:** Vancomycin is an antibiotic used to treat infections caused by gram-positive organisms that are resistant to beta-lactam antibiotics, such as methicillin-resistant staphylococci (MRSA), Streptococcus viridans group, penicillin/cephalosporin-resistant S pneumoniae, and penicillin/ampicillin-resistant Enterococcus species. The oral formulation, which is not absorbed, is used in the treatment of pseudomembranous colitis caused by Clostridium difficile. Vancomycin is also used when patients are intolerant or allergic to beta lactams. Vancomycin has been associated with nephrotoxicity and ototoxicity, although it appears that many of these reports reflected impurities in early formulations. Monitoring of vancomycin-related nephrotoxicity is recommended only for patients with reduced renal function, those receiving aggressive or prolonged vancomycin regimens, or those at high-risk including patients comedicated with other nephrotoxic agents. Trough concentrations are recommended for therapeutic monitoring of vancomycin, preferably acquired at steady-state (just before fourth dose). To avoid development of resistance, vancomycin trough levels should remain above 10.0 mcg/mL. Complicated infections require higher target levels, typically 15.0 to 20.0 mcg/mL. Peak concentrations do not correlate well to efficacy or nephrotoxicity, but may be useful for pharmacokinetic analyses (eg, area under the curve: AUC studies) or for select patients.

**Useful For:** Preferred test for monitoring vancomycin therapy Monitoring trough concentrations drawn at steady-state in selected patients receiving vancomycin therapy

**Interpretation:** Trough levels correlate better with efficacy than peak levels, with target trough levels of 10.0 to 20.0 mcg/mL, depending on the type of infection. These levels are consistent with Mayo Clinic Antimicrobial Therapy Guidelines.

**Reference Values:** Therapeutic: 10.0-20.0 mcg/mL


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**Vancomycin-Resistant Enterococcus, Molecular Detection, PCR**

**Clinical Information:** Vancomycin-resistant enterococci (VRE) are major nosocomial pathogens. Patients who are particularly vulnerable to fatal disease from VRE include those with hematomic malignancies and liver transplants. Nosocomial spread of VRE occurs as the result of fecal carriage. Risks for both colonization and infection include prolonged hospitalization, intensive care unit stay, transplantation, hematomic malignancies, and prolonged exposure to antibiotics. The Centers for Disease Control and Prevention provides recommendations to prevent the spread of VRE in institutional settings. These recommendations include isolation of patients experiencing active VRE infection, screening of patients by perianal swab or fecal testing to identify carriers of VRE, and subsequent isolation or cohorting of VRE carriers. Identification and isolation of VRE carriers has been shown to be cost-effective. In Enterococcus faecalis or E faecium, vancomycin resistance is usually associated with the presence of the vanA or vanB genes. The presence of these genes is detected by a molecular method in this assay.

**Useful For:** Identifying carriers of vancomycin-resistant enterococci

**Interpretation:** Positive test results indicate the presence of either the vanA or vanB gene, which confers vancomycin resistance in Enterococcus faecalis and Enterococcus faecium (and occasionally other organisms). Patients with a positive test result should be placed in isolation or cohorted with other vancomycin-resistant enterococci (VRE) carriers according to the institution's infection control practices. A negative result indicates the absence of detectable vanA or vanB DNA in the specimen but does not rule-out carrier status as false-negative results may occur due to inhibition of PCR, sequence variability underlying primers or probes, or the presence of VRE in quantities less than the limit of detection of the assay. In the rare event that PCR testing appears to be negative but there is evidence of
PCR inhibition, the result will read "PCR inhibition present," in such a case, a new specimen should be submitted for repeat testing.

**Reference Values:**
Not applicable

**Clinical References:**

FVANG

**Vanilla IgG**

**Interpretation:** mcg/mL of IgG  
Lower Limit of Quantitation 2.0  
Upper Limit of Quantitation 200

**Reference Values:**
<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

VANIL

**Vanilla, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L  Interpretation

Vanillylmandelic Acid (VMA) and Homovanillic Acid (HVA), Random, Urine

Clinical Information: Elevated values of homovanillic acid (HVA), vanillylmandelic acid (VMA), and other catecholamine metabolites (eg, dopamine) may be suggestive of the presence of a catecholamine-secreting tumor (eg, neuroblastoma, pheochromocytoma, or other neural crest tumors). HVA and VMA levels may also be useful in monitoring patients who have been treated as a result of the above-mentioned tumors. HVA levels may also be altered in disorders of catecholamine metabolism: monamine oxidase-A deficiency can cause decreased urinary HVA values, while a deficiency of dopamine beta-hydrolase (the enzyme that converts dopamine to norepinephrine) can cause elevated urinary HVA values.

Useful For: First preferred test for screening for catecholamine-secreting tumors in a random urine specimen when requesting both homovanillic acid and vanillylmandelic acid Supporting a diagnosis of neuroblastoma Monitoring patients with a treated neuroblastoma

Interpretation: Homovanillic acid (HVA) and vanillylmandelic acid (VMA) concentrations are elevated in more than 90% of patients with neuroblastoma; both tests should be performed. A positive test could be due to a genetic or nongenetic condition. Additional confirmatory testing is required. A normal result does not exclude the presence of a catecholamine-secreting tumor. Elevated HVA and VMA values are suggestive of a pheochromocytoma, but they are not diagnostic.

Reference Values:

VANILLYL MANDELIC ACID
<1 year: <25.0 mg/g creatinine
1 year: <22.5 mg/g creatinine
2-4 years: <16.0 mg/g creatinine
5-9 years: <12.0 mg/g creatinine
10-14 years: <8.0 mg/g creatinine
> or =15 years: <7.0 mg/g creatinine

HOMOVANILIC ACID
<1 year: <35.0 mg/g creatinine
1 year: <30.0 mg/g creatinine
2-4 years: <25.0 mg/g creatinine
5-9 years: <15.0 mg/g creatinine
10-14 years: <9.0 mg/g creatinine
> or =15 years: <8.0 mg/g creatinine


**VMA**

**Vanillylmandelic Acid (VMA), 24 Hour, Urine**

**Clinical Information:** Vanillylmandelic acid (VMA) and other catecholamine metabolites (homovanillic acid [HVA] and dopamine) are typically elevated in patients with catecholamine-secreting tumors (eg, neuroblastoma, pheochromocytoma, and other neural crest tumors). VMA and HVA levels may also be useful in monitoring patients who have been treated as a result of one of the above-mentioned tumors.

**Useful For:** Screening children for catecholamine-secreting tumors with a 24-hour urine collection when requesting testing for only vanillylmandelic acid Supporting a diagnosis of neuroblastoma Monitoring patients with a treated neuroblastoma

**Interpretation:** Vanillylmandelic acid and/or homovanillic acid concentrations are elevated in most patients (more than 90%) with neuroblastoma; both tests should be performed. A positive test could be due to a genetic or nongenetic condition. Additional confirmatory testing is required. A normal result does not exclude the presence of a catecholamine-secreting tumor. Elevated values are suggestive of a pheochromocytoma, but they are not diagnostic.

**Reference Values:**

- <1 year: <25.0 mg/g creatinine
- 1 year: <22.5 mg/g creatinine
- 2-4 years: <16.0 mg/g creatinine
- 5-9 years: <12.0 mg/g creatinine
- 10-14 years: <8.0 mg/g creatinine
- > or =15 years (adults): <8.0 mg/24 hours


**VMAR**

**Vanillylmandelic Acid (VMA), Random, Urine**

**Clinical Information:** Vanillylmandelic acid (VMA) and other catecholamine metabolites (homovanillic acid [HVA] and dopamine) are typically elevated in patients with catecholamine-secreting tumors (eg, neuroblastoma, pheochromocytoma, and other neural crest tumors). VMA and HVA levels may also be useful in monitoring patients who have been treated as a result of one of the above-mentioned tumors.

**Useful For:** Screening children for catecholamine-secreting tumors with a random urine collection when requesting vanillylmandelic acid only Supporting a diagnosis of neuroblastoma Monitoring patients with a treated neuroblastoma
Interpretation: Vanillylmandelic acid (VMA) and/or homovanillic acid concentrations are elevated in more than 90% of patients with neuroblastoma; both tests should be performed. A positive test could be due to a genetic or nongenetic condition. Additional confirmatory testing is required. A normal result does not exclude the presence of a catecholamine-secreting tumor. Elevated VMA values are suggestive of a pheochromocytoma, but they are not diagnostic.

Reference Values:
<1 year: <25.0 mg/g creatinine
1 year: <22.5 mg/g creatinine
2-4 years: <16.0 mg/g creatinine
5-9 years: <12.0 mg/g creatinine
10-14 years: <8.0 mg/g creatinine
> or =15 years (adults): <7.0 mg/g creatinine

Clinical References:

Varicella Zoster Virus (VZV) Immunostain, Technical Component Only

Clinical Information: Varicella zoster virus (VZV) is a member of the herpes virus family and is the etiological agent for varicella (chicken pox) and herpes zoster (shingles). The immunostain for VZV uses a cocktail of antibodies that recognizes several glycoproteins, the nucleocapsid protein, and the immediate early protein of the virus.

Useful For: Aids in the identification of varicella zoster virus infection

Interpretation: This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Clinical References:

Varicella-Zoster Antibody, IgG, Serum

Clinical Information: Varicella-zoster virus (VZV), a herpes virus, causes 2 distinct exanthematous (rash-associated) diseases: chickenpox (varicella) and herpes zoster (shingles).
Chickenpox is a highly contagious, though typically benign disease, usually contracted during childhood. Chickenpox is characterized by a dermal vesiculopustular rash that develops in successive crops approximately 10 to 21 days following exposure. Although primary infection with VZV results in immunity and protection from subsequent infection, VZV remains latent within sensory dorsal root ganglia and upon reactivation, manifests as herpes zoster or shingles. During reactivation, the virus migrates along neural pathways to the skin, producing a unilateral rash, usually limited to a single dermatome. Shingles is an extremely painful condition typically occurring in older nonimmune adults or those with waning immunity to VZV and in patients with impaired cellular immunity. Individuals at risk for severe complications following primary VZV infection include pregnant women, in whom the virus may spread through the placenta to the fetus, causing congenital disease in the infant. Additionally, immunosuppressed patients are at risk for developing severe VZV-related complications, which include cutaneous disseminated disease and visceral organ involvement. Serologic screening for IgG-class antibodies to VZV aids in identifying nonimmune individuals.

**Useful For:** Determination of immune status of individuals to the varicella-zoster virus (VZV)

**Documentation of previous infection with VZV in an individual without a previous record of immunization to VZV**

**Interpretation:**
- **Positive:** Antibody index value (AI) of 1.1 or higher: The reported AI value is for reference only. This is a qualitative test and the numeric value of the AI is not indicative of the amount of antibody present. AI values above the manufacturer recommended cutoff for this assay indicate that specific antibodies were detected, suggesting prior exposure or vaccination. The presence of detectable IgG-class antibodies indicates prior exposure to the varicella-zoster virus (VZV) through infection or immunization. Individuals testing positive are considered immune to varicella-zoster. Equivocal: AI 0.9-1.0 Submit an additional specimen for testing in 10 to 14 days to demonstrate IgG seroconversion if recently vaccinated or if otherwise clinically indicated. Negative: AI of 0.8 or lower The absence of detectable IgG-class antibodies suggests no prior exposure to the VZV or the lack of a specific immune response to immunization.

**Reference Values:**
- **Vaccinated:** Positive (> or =1.1 AI)
- **Unvaccinated:** Negative (< or =0.8 AI)

**Reference values apply to all ages.**

**Clinical References:**

**Varicella-Zoster Antibody, IgM and IgG (Separate Determinations), Serum**

**Clinical Information:** Varicella-zoster virus (VZV), a herpesvirus, causes 2 distinct exanthematous (rash-associated) diseases: chickenpox (varicella) and shingles (herpes zoster). Chickenpox is a highly contagious, though typically benign disease, usually contracted during childhood. Chickenpox is characterized by a dermal vesiculopustular rash that develops in successive crops approximately 10 to 21 days following exposure. Although primary infection with VZV results in immunity and protection from subsequent infection, VZV remains latent within sensory dorsal root ganglia and upon reactivation, manifests as herpes zoster or shingles. During reactivation, the virus migrates along neural pathways to the skin, producing a unilateral rash, usually limited to a single dermatome. Shingles is an extremely painful condition typically occurring in older nonimmune adults or those with waning immunity to VZV and in patients with impaired cellular immunity. Individuals at risk for severe complications following primary VZV infection include pregnant women, in whom the virus may spread through the placenta to the fetus causing congenital disease in the infant. Additionally, immunosuppressed patients are at risk for developing severe VZV-related complications, which include cutaneous disseminated disease and visceral organ involvement. Serologic screening for IgG-class antibodies to VZV will aid in identifying nonimmune individuals.
nonimmune individuals. The presence of IgM-class antibodies to VZV is suggestive of acute or recent infection however results should be correlated with clinical presentation.

**Useful For:** Laboratory diagnosis of acute and recent infection with varicella-zoster virus (VZV) 
Determination of immune status of individuals to the VZV Documentation of previous infection with VZV in an individual without a previous record of immunization to VZV

**Interpretation:** A positive IgG result coupled with a positive IgM result suggests recent infection with varicella-zoster virus (VZV). This result should not be used alone to diagnose VZV infection and should be interpreted in the context of clinical presentation. A positive IgG result coupled with a negative IgM result indicates previous vaccination to or infection with VZV. These individuals are considered to have protective immunity to re-infection. A negative IgG result coupled with a negative IgM result indicates the absence of prior exposure to VZV and nonimmunity. However, a negative result does not rule-out VZV infection. The specimen may have been drawn before the appearance of detectable antibodies. Negative results in suspected early VZV infections should be followed by testing a new serum specimen in 2 to 3 weeks. Equivocal results should be followed up with testing of a new serum specimen within 10 to 14 days.

**Reference Values:**

**IgM**
Negative
Reference values apply to all ages.

**IgG**
Vaccinated: positive (> or =1.1 AI)
Unvaccinated: negative (< or =0.8 AI)
Reference values apply to all ages.

**Clinical References:**

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**Varicella-Zoster Virus (VZV) Antibody, IgM, Serum**

**Clinical Information:** Varicella-zoster virus (VZV), a herpes virus, causes 2 exanthematous (rash-associated) diseases, chickenpox and herpes zoster (shingles). Chickenpox is a highly contagious disease usually contracted during childhood and is characterized by a dermal vesiculopustular rash that develops in successive crops. Although primary infection results in immunity to subsequent exposure to chickenpox, the virus remains latent in the body, localized to the dorsal root or cranial nerve ganglia. Reactivation of latent infection manifests as herpes zoster. On reactivation, the virus migrates along neural pathways to the skin, producing a unilateral rash usually limited to a single dermatome. Reactivation occurs in older adults and in patients with impaired cellular immunity. Several populations are at risk of suffering unusually severe reactions to VZV infections. The infection in pregnant women may spread through the placenta to the fetus causing congenital disease in the infant. Immunocompromised patients in hospitals may contract severe nosocomial infections from others who have active VZV infections. Therefore, serologic screening of direct health care providers (physicians, allied health care personnel) and individuals in high-risk groups is necessary to avoid uncontrolled spread of infection. While the clinical presentation of VZV infection is generally characteristic, serologic evaluation of patients with atypical and systemic infections is often required. For example, it is extremely important to serologically evaluate patients for the early detection of VZV infections in hospital settings. Nosocomial spread of VZV infection can be life-threatening to immunocompromised patients susceptible to infection.

**Useful For:** Diagnosing acute-phase infection with varicella-zoster virus

**Interpretation:** A positive IgM result indicates a recent infection with varicella-zoster virus (VZV).
A negative result does not rule out the diagnosis of VZV infection. The specimen may have been drawn before the appearance of detectable antibodies. Negative results in suspected early VZV infection should be followed by testing a new specimen in 2 to 3 weeks.

**Reference Values:**

Negative

Reference values apply to all ages.

**Clinical References:**

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**FVZGC**

**Varicella-Zoster Virus Antibody, IgG, CSF**

**Interpretation:** The detection of antibodies to varicella-zoster in CSF may indicate central nervous system infection. However, consideration must be given to possible contamination by blood or transfer of serum antibodies across the blood-brain barrier.

**Reference Values:**

- 134 IV or less: Negative - No significant level of IgG antibody to varicella-zoster virus detected.
- 135 - 165 IV: Equivocal - Repeat testing in 10 - 14 days may be helpful.
- 166 IV or greater: Positive – IgG antibody to varicella-zoster virus detected, which may indicate a current or past varicella-zoster infection.

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**LVZV**

**Varicella-Zoster Virus, Molecular Detection, PCR**

**Clinical Information:** Varicella-zoster virus (VZV) causes both varicella (chickenpox) and herpes zoster (shingles). VZV produces a generalized vesicular rash on the dermis (chickenpox) in normal children, usually before 10 years of age. After primary infection with VZV, the virus persists in latent form and may emerge clinically (usually in adults 50 years of age and older) to cause a unilateral vesicular eruption, generally in a dermatomal distribution (shingles).

**Useful For:** Rapid (qualitative) detection of varicella-zoster virus DNA in clinical specimens for laboratory diagnosis of disease due to this virus

**Interpretation:** Detection of varicella-zoster virus (VZV) DNA in clinical specimens supports the clinical diagnosis of infection due to this virus. VZV DNA is not detected in cerebrospinal fluid from patients without central nervous system disease caused by this virus. This LightCycler PCR assay does not yield positive results with other herpesvirus gene targets (herpes simplex virus, cytomegalovirus, Epstein-Barr virus).

**Reference Values:**

Negative

**Clinical References:**
**Vascular Endothelial Growth Factor (VEGF), Plasma**

**Clinical Information:** Vascular endothelial growth factor (VEGF) is a critical modulator of angiogenesis (the growth of new blood vessels).(1) In mammals, there are 5 members of the VEGF family, with VEGF-A being the most well-studied. VEGF-A promotes angiogenesis by inducing migration of endothelial cells, promoting mitosis of endothelial cells, and upregulating matrix metalloproteinase activity.(2) VEGF-A is regulated by hypoxia, with increased expression when cells detect an environment low in oxygen. Physiologically, VEGF induces new blood vessel formation during embryonic development, after tissue injury, and in response to blocked vessels. VEGF also regulates pathological vessel formation, such as in tumor growth and metastases. Angiogenesis during tumor development is complex, although it is clear that VEGF plays a key role. VEGF also regulates angiogenesis in other disease states including rheumatoid arthritis (RA), osteoarthritis, diabetes, and age-related macular degeneration.(3) In addition, circulating concentrations of VEGF are elevated in patients with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome, a monoclonal plasma cell disorder.(4) Although the pathologic role of VEGF in POEMS is unclear, it is a useful diagnostic marker for assessing response to therapy.

**Useful For:** Evaluation of patients with suspected POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, particularly in differentiating from other forms of polyneuropathy and monoclonal plasma cell disorders Monitoring response to treatment in patients with a known diagnosis of POEMS syndrome

**Interpretation:** Elevated concentration of vascular endothelial growth factor (VEGF) may be consistent with a diagnosis of POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome. Decreasing concentrations of VEGF over time in a patient with POEMS syndrome may be consistent with a therapeutic response.

**Reference Values:**
< or =96.2 pg/mL


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**Vasoactive Intestinal Polypeptide (VIP), Plasma**

**Clinical Information:** Vasoactive intestinal polypeptide (VIP) was originally isolated from porcine small intestine and was recognized by its potent vasodilator activity. This brain/gut hormone has widespread distribution and is present in neuronal cell bodies localized in the central nervous system, digestive, respiratory, and urogenital tracts, exocrine glands, and thyroid and adrenal glands. VIP has a wide scope of biological actions. The main effects of VIP include relaxation of smooth muscle (bronchial and vascular dilation), stimulation of gastrointestinal water and electrolyte secretion, and release of pancreatic hormones. VIP-producing tumors (VIPomas) are rare; most (90%) are located in the pancreas. Watery diarrhea, hypokalemia, and achlorhydria are key symptoms.

**Useful For:** Detection of vasoactive intestinal polypeptide producing tumors in patients with chronic diarrheal diseases

**Interpretation:** Values >75 pg/mL may indicate the presence of an enteropancreatic tumor causing hypersecretion of vasoactive intestinal polypeptide (VIP). Values >200 pg/mL are strongly suggestive of VIP-producing tumors (VIPoma). VIPoma is unlikely with a 24-hour stool volume <700 mL.

**Reference Values:**

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*Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLabaratories.com*
**Clinical References:**

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**Vasoactive Intestine Polypeptide (VIP), Immunostain Without Interpretation**

**Clinical Information:** Excessive vasoactive intestine polypeptide (VIP) production by islet cell tumors has been associated with Verner-Morrison syndrome, also known as pancreatic cholera, in which patients have massive, watery diarrhea. A subset of normal cells in the pancreatic islets express VIP (<1%). Peripheral nerves and ganglion cells also serve as a positive internal control.

**Useful For:** Aids in the identification of islet cell tumors

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**VDRL, Spinal Fluid**

**Clinical Information:** The Venereal Disease Research Laboratory (VDRL) is a nontreponemal serologic test for syphilis that uses a cardiolipin-cholesterol-lecithin antigen to detect reaginic antibodies. The VDRL test performed on cerebrospinal fluid (CSF) can be used to diagnose neurosyphilis in patients with a prior history of syphilis infection. The presence of neurosyphilis in untreated patients can be detected by the presence of pleocytosis, elevated protein, and a positive VDRL.

**Useful For:** Aiding in the diagnosis of neurosyphilis

**Interpretation:** A positive Venereal Disease Research Laboratories (VDRL) on spinal fluid is highly specific for neurosyphilis. A single negative VDRL result should not be used to exclude neurosyphilis and repeat testing on a new specimen may be necessary. Positive results will be titered.

**Reference Values:**
Negative
Reference values apply to all ages.

**Clinical References:** Miller JN: Value and limitations of nontreponemal and treponemal tests in the laboratory diagnosis of syphilis. Clin Obstet Gynecol 1975;18:191-203
Vedolizumab Quantitation with Antibodies, Serum

**Clinical Information:** Vedolizumab (Entyvio) is a humanized monoclonal antibody directed against integrin alpha-4 beta-7. Blocking the alpha-4 beta-7 integrin results in a gut-selective anti-inflammatory response. The drug is FDA-approved for the treatment of adult patients with moderately to severely active ulcerative colitis or Crohn disease. Although optimal therapeutic concentrations of vedolizumab are not well known, Mayo Clinic Gastroenterologists are working to correlate drug concentrations with patient outcomes. Vedolizumab testing will assess the patients loss of response to therapy, similar to therapy received using tumor necrosis factor (TNF) inhibitors, such as infliximab and adalimumab. Some patients on vedolizumab may develop antibodies-to-vedolizumab (ATV) over time. In clinical trials, approximately 4% of patients treated with vedolizumab were positive for ATV at any time and 1% or less were persistently positive. Therefore, simultaneous testing for measurement of ATV is recommended. ATV uses a bridging immunoassay on an electrochemiluminescence (Mesoscale Discovery) platform.

**Useful For:** Assessing the unexpected loss of response to therapy with vedolizumab over time An aid to achieving desired serum levels of vedolizumab

**Interpretation:** Data in the literature with association of vedolizumab trough levels and improved outcomes is still scarce. The limit of quantitation of the test is 2.0 mcg/mL. In a retrospective Mayo Clinic study conducted from 2016-2017 with 171 patients (62% Crohn disease, 31% ulcerative colitis, and 7% indeterminate colitis), the median vedolizumab trough concentration was 15.3 mcg/mL. Minimum trough (immediately before next infusion) therapeutic concentrations of vedolizumab are expected to be above 15 mcg/mL.

**Reference Values:**
Vedolizumab lower limit of quantitation=2.0 mcg/mL

Antibodies-To-Vedolizumab: <9.8 ng/mL

(ATV) over time. In clinical trials, approximately 4% of patients treated with vedolizumab were positive for ATV at any time and 1% or less were persistently positive. Therefore, simultaneous testing for measurement of ATV is recommended. ATV uses a bridging immunoassay on an electrochemiluminescence (Mesoscale Discovery) platform.

**Useful For:** Assessing the response to therapy with vedolizumab An aid to achieving desired trough serum levels of vedolizumab Monitoring patient compliance

**Interpretation:** Data in the literature with association of vedolizumab trough levels and improved outcomes is still scarce. The limit of quantitation of the test is 2.0 mcg/mL. In a retrospective Mayo Clinic study conducted from 2016-2017 with 171 patients (62% Crohn disease, 31% ulcerative colitis, and 7% indeterminate colitis), the median vedolizumab trough concentration was 15.3 mcg/mL. Minimum trough (immediately before next infusion) therapeutic concentrations of vedolizumab are expected to be above 15 mcg/mL.

**Reference Values:**
Vedolizumab lower limit of quantitation: 2.0 mcg/mL

**Clinical References:**

VELV

**Velvet Leaf, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.
Reference Values:
Class IgE kU/L  Interpretation
0  Negative
1  0.35-0.69  Equivocal
2  0.70-3.49  Positive
3  3.50-17.4  Positive
4  17.5-49.9  Strongly positive
5  50.0-99.9  Strongly positive
6  > or =100  Strongly positive Reference values apply to all ages.


VENLA 83732
Venlafaxine, Serum
Clinical Information: Venlafaxine is a serotonin and norepinephrine reuptake inhibitor approved for treatment of major depression, anxiety and panic disorders, and social phobias. It is also used for bipolar disorder, bulimia, post-traumatic stress, obsessive behavior, and attention-deficit disorder. Venlafaxine is converted by CYP2D6 to the active metabolite, O-desmethylvenlafaxine. The therapeutic range for venlafaxine includes measurement if O-desmethylvenlafaxine; optimal response is seen when combined concentrations of parent and metabolite are between 195 and 400 ng/mL. Venlafaxine is significantly affected by reduced hepatic function, but only slightly by reduced renal function. Average elimination half-lives are 5 hours for venlafaxine and 10 hours for O-desmethylvenlafaxine, which are much shorter than many other antidepressants. For this reason, extended release formulations are available. Time to peak serum concentration is 2 hours for the regular product and 8 hours for the extended release product. Common toxicities are mild, including drowsiness, dizziness, nausea, and headache.

Useful For: Monitoring serum concentration during therapy Evaluating potential toxicity The test may also be used to evaluate patient compliance.

Interpretation: Most individuals display optimal response to venlafaxine when combined serum levels of venlafaxine and O-desmethylvenlafaxine are between 195 and 400 ng/mL. Some individuals may respond well outside of this range, or may display toxicity within the therapeutic range, thus interpretation should include clinical evaluation. Risk of toxicity is increased with combined levels >1,000 ng/mL. Therapeutic ranges are based on specimens drawn at trough (ie, immediately before the next dose).

Reference Values:
Venlafaxine + O-desmethylvenlafaxine: 195-400 ng/mL


FBMBLBombus terrestrus) IgE 57975
Venom Bumble Bee (Bombus terrestrus) IgE
Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10-0.34 Equivocal/Borderline 1 0.35-0.69 Low Positive 2 0.70-3.49 Moderate Positive 3 3.50-17.49 High Positive 4 5 6 17.50-49.99

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**VLCZ 35571**

**Very Long Chain Acyl-CoA Dehydrogenase Deficiency, Full Gene Analysis**

**Clinical Information:** Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency is an autosomal recessive disorder of mitochondrial fatty acid beta-oxidation. Mitochondrial beta-oxidation plays a major role in energy production and VLCAD catalyzes the first step in the breakdown of fatty acids that are 14 to 20 carbons long. VLCAD deficiency has a reported incidence of approximately 1 in 30,000 births and has a variable age of onset that is generally classified into 3 categories. Individuals with the early-onset type present with cardiomyopathy, hypotonia, and hepatomegaly in the first months of life; sudden death is also frequent. Individuals with the early-childhood onset type typically present with hypoketotic hypoglycemia and hepatomegaly without cardiomyopathy. Individuals with the late-onset type of VLCAD deficiency generally present after childhood with intermittent rhabdomyolysis and muscle dysfunction that often manifests as muscle cramps and exercise intolerance. Review of clinical features and biochemical analysis via plasma acylcarnitines, plasma fatty acid profile, urine organic acids, and fibroblast fatty acid oxidation probe studies are recommended as laboratory evaluations for VLCAD deficiency. Plasma and urine biochemical testing are not reliable for identifying all individuals with VLCAD deficiency or confirming carrier status, as biochemical findings may normalize during periods of good metabolic control. It is uncertain whether skin fibroblast analysis can identify carriers of VLCAD deficiency. The diagnosis is confirmed by molecular testing. Mutations in the ACADVL gene are responsible for VLCAD deficiency. Most mutations are family specific with the exception of the V283A mutation (also reported in the literature as V243A). This mutation is estimated to account for 20% of pathogenic alleles in patients identified by newborn screening. When this test is ordered, results of biochemical assays should be included with the specimen as they are necessary for accurate interpretation.
of the VLCAD sequence analysis.

**Useful For:** Confirmation of a diagnosis of very long chain acyl-CoA dehydrogenase (VLCAD) deficiency Carrier screening in cases where there is a family history of VLCAD deficiency, but an affected individual is not available for testing or disease-causing mutations have not been identified

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**VHL Gene, Erythrocytosis Mutation Analysis**

**Clinical Information:** Erythrocytosis (ie, increased RBC mass or polycythemia) may be primary, due to an intrinsic defect of bone marrow stem cells (ie, polycythemia vera, or secondary, in response to increased serum erythropoietin levels). Secondary erythrocytosis is associated with a number of disorders including chronic lung disease, chronic increase in carbon monoxide (due to smoking), cyanotic heart disease, high-altitude living, renal cysts and tumors, hepatoma, and other Epo-secreting tumors. When these common causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be suspected. Unlike polycythemia vera, hereditary erythrocytosis is not associated with the risk of clonal evolution and should present with isolated erythrocytosis that has been present since birth. A small subset of cases is associated with pheochromocytoma and paraganglioma formation. It is caused by mutations in several genes, including VHL, and may be inherited in either an autosomal dominant or autosomal recessive manner. A family history of erythrocytosis would be expected in these cases, although it is possible for new mutations to arise in an individual. The genes coding for hemoglobin, hemoglobin-stabilization proteins (2,3 bisphosphoglycerate mutase: BPGM), the erythropoietin receptor (EPOR), and oxygen-sensing pathway enzymes (hypoxia-inducible factor: HIF/EPAS1, prolyl hydroxylase domain: PHD2/EGLN1, and VHL can result in hereditary erythrocytosis (see Table). High-oxygen-affinity hemoglobin variants and BPGM abnormalities result in a decreased p50 result, whereas those affecting EPOR, HIF, PHD, and VHL typically have normal p50 results. The true prevalence of hereditary erythrocytosis causing mutations is unknown. Genes Associated with Hereditary Erythrocytosis Gene Inheritance Serum Epo p50 JAK2 V617F Acquired Decreased Normal JAK2 exon 12 Acquired Decreased Normal EPOR Dominant Decreased to normal level Normal PHD2/EGLN1 Dominant Normal level Normal BPGM Recessive Normal level Decreased Beta Globin Dominant Normal level to increased Decreased Alpha Globin Dominant Normal level to increased Decreased HIF2A/EPAS1 Dominant Normal level to increased Normal VHL Recessive Normal to increased Normal The oxygen-sensing pathway functions through an enzyme, hypoxia-inducible factor (HIF), which regulates RBC mass. A heterodimer protein comprised of alpha and beta subunits, HIF functions as a marker of depleted oxygen concentration. When present, oxygen becomes a substrate-mediating HIF-alpha subunit degradation. In the absence of oxygen, degradation does not take place and the alpha protein component is available to dimerize with a HIF-beta subunit. The heterodimer then induces transcription of many hypoxia response genes including EPO, VEGF, and GLUT1. HIF-alpha is regulated by von Hippel-Lindau (VHL) protein-mediated ubiquitination and proteasomal degradation, which requires prolyl hydroxylation of HIF proline residues. Mutations resulting in altered VHL proteins can lead to familial erythrocytosis, type 2 (ECYT2; OMIM 263400). ECYT2 is a clinically heterogeneous disorder characterized by congenital erythrocytosis with or without high serum EPO levels, venous and arterial thrombosis, and
pulmonary hypertension that can manifest as early as infancy but more typically into adulthood. An increased risk for tumors associated with von Hippel-Lindau syndrome, which is also caused by mutations in the VHL gene, has not been observed.

**Useful For:** Diagnosis of suspected JAK2-negative VHL-related erythrocytosis associated with lifelong sustained increased RBC mass, elevated RBC count, hemoglobin, or hematocrit

**Interpretation:** Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

**Reference Values:**
Only orderable as part of a profile. For more information see HEMP / Hereditary Erythrocytosis Mutations.

An interpretive report will be provided.

**Clinical References:**

**VHLZ 37440**

**VHL Gene, Full Gene Analysis**

**Clinical Information:** von Hippel-Lindau (VHL) disease is an autosomal dominant cancer predisposition syndrome with a prevalence of approximately 1 in 36,000 livebirths. It predisposes affected individuals to the development of mainly 5 different types of neoplasms: retinal angioma (approximately 5%-70% penetrance), cerebellar hemangioblastoma (CHB) (44%-72% penetrance), clear-cell renal cell carcinoma (cRCC) (approximately 25%-60% penetrance), spinal hemangioblastoma (SHB) (approximately 13%-50% penetrance), and pheochromocytoma (PC) (approximately 10%-20% penetrance). Angiomas in other organs, pancreatic cysts/adenomas/carcinomas, islet cell tumors, and endolymphatic sac tumors can also occur. VHL-related tumors typically present in the second to third decade of life, but sometimes earlier, particularly for retinal angiomas. For each tumor type, the incidence rates rise steadily, albeit at different slopes, throughout life. VHL disease is caused by heterozygous germline loss-of-function sequence variants, small deletions or insertions (approximately 80% of cases), or large germline deletions (approximately 20% of cases) of the VHL gene. Approximately 20% of cases are due to new (de novo) pathogenic variants, which in some cases result in disease mosaicism. This presents a diagnostic challenge for individuals who present with clinical signs of VHL disease, but test negative genetically because the pathogenic variant is not present in all peripheral leukocytes. VHL encodes the VHL protein, a tumor suppressor protein that is involved in ubiquitination and degradation of a variety of other proteins, most notably hypoxia-inducible factor (HIF). HIF induces expression of genes that promote cell survival and angiogenesis under conditions of hypoxia. It is believed that diminished HIF degradation due to inactive VHL protein causes the tumors in VHL disease. Tumors form when the remaining intact copy of VHL is somatically inactivated in target tissues (2-hit model). Sporadic cRCC, unrelated to VHL disease, also shows somatic deletions, sequence variants, or aberrant methylation in 80% to 100% of cases. Retinal angioma, CHB, and SHB cause morbidity and some mortality through...
pressure on adjacent structures and through retinal or subarachnoid hemorrhages. VHL-related cRCC and PC follow a similar clinical course as their sporadic counterparts, with substantial morbidity and mortality. Early detection of VHL-related tumors can reduce these adverse outcomes, and surveillance of affected individuals is, therefore, widely advocated. Genetic testing is the most accurate way to identify presymptomatic individuals, who can then be entered into a surveillance program. Research has suggested that certain combinations of VHL tumors cluster in VHL families, and this may be driven by the type of VHL gene variant present in the family. This observation has led to a phenotype-based classification of VHL syndrome. However, it should be noted that these patterns are not clear cut, and should not necessarily be used for diagnostic or therapeutic purposes.

VHL Type 1: Retinal angioma, central nervous system (CNS) hemangioblastoma, renal cell carcinoma, pancreatic cysts, and neuroendocrine tumors. Low risk for pheochromocytoma. Associated with pathogenic truncating or missense variants that are predicted to grossly disrupt the folding of VHL protein. VHL Type 2: Pheochromocytoma, retinal angiomas, and CNS hemangioblastomas. High risk for pheochromocytoma. Associated with pathogenic missense variants. VHL Type 2 is further subdivided: -Type 2A: Pheochromocytoma, retinal angiomas, and CNS hemangioblastomas; low risk for renal cell carcinoma -Type 2B: Pheochromocytoma, retinal angiomas, CNS hemangioblastomas, pancreatic cysts, and neuroendocrine tumor; high risk for renal cell carcinoma -Type 2C: Risk for pheochromocytoma only

Additionally, pathogenic sequence variants distinct from those associated with VHL syndrome can cause hereditary erythrocytosis or polycythemia. Cases of VHL disease and erythrocytosis are largely mutually exclusive, and patients who present with erythrocytosis do not typically develop the neoplasms discussed above, although they are sometimes associated with varicose veins and vertebral hemangiomas. Erythrocytosis due to VHL is caused by germline homozygous or compound heterozygous pathogenic sequence variants, and is inherited in an autosomal recessive manner. These patients usually have a markedly high erythropoietin level in the presence of an elevated hematocrit. Erythrocytosis due to a germline homozygous missense variant at nucleotide c.598C->T, p.R200W in the VHL gene has been found endemically in the Chuvash region of Russia, leading individuals with this variant to be labeled as having Chuvash polycythemia (CP), although further studies have determined that this variant can be found in other ethnic groups as well. These patients are at an increased risk to develop cerebrovascular and embolic complications. Heterozygous carriers are typically unaffected.

Useful For: Diagnosis of suspected von Hippel-Lindau (VHL) disease Diagnosis of suspected VHL-related hereditary erythrocytosis

Interpretation: Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Reference Values: An interpretive report will be provided.


**VIBC**

**Vibrio Culture, Stool**

Clinical Information: Diarrhea may be caused by a number of agents (eg, bacteria, viruses, parasites, and chemicals) and these agents may result in similar symptoms. A thorough patient history covering symptoms, severity and duration of illness, age, travel history, food consumption, history of recent antibiotic use, and illnesses in the family or other contacts will help the physician determine the appropriate testing to be performed. Vibrio cholerae, the causative agent of endemic, epidemic, and pandemic cholera, results in large volumes of rice-water stools due to the production of an enterotoxin. Severe dehydration is of concern in patients without access to adequate medical care. In the United States, Vibrio parahemolyticus is the most common cause of Vibrio disease. Vibrio parahemolyticus is associated with the consumption of raw shellfish or fish and results in gastroenteritis with nausea, vomiting, abdominal cramps, low-grade fever, and chills. Usually rehydration is the only treatment required, although in some cases, antimicrobial therapy is needed.

**Useful For:** Determining whether Vibrio species is the cause of diarrhea and, in turn, identifying the source of the infectious agent

**Interpretation:** The growth of Vibrio species identifies the cause of diarrhea.

**Reference Values:**
No growth


**VIGA**

**Vigabatrin (Sabril)**

Reference Values:
Units: ug/mL

Therapeutic and toxic ranges have not been established.

Expected serum vigabatrin concentrations in patients receiving recommended daily dosages: 20 â€“ 160 ug/mL

**VIM**

**Vimentin (VIM) Immunostain, Technical Component Only**

Clinical Information: Vimentin is an intermediate filament protein (57 kD) present in cells of mesenchymal origin. A number of tumors coexpress vimentin and cytokeratin (eg, thyroid carcinomas, pleomorphic adenomas of the salivary glands, and some renal carcinomas). Coexpression of desmin and vimentin has also been reported in a number of soft tissue tumors (eg, rhabdomyosarcomas, leiomyosarcomas and alveolar soft tissue sarcomas).

**Useful For:** Identification of cells of mesenchymal origin in normal and neoplastic tissues

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be
performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

**VIRNR**
87266

**Viral Culture, Non-Respiratory**

**Clinical Information:** Viruses are responsible for a broad spectrum of clinical symptoms and diseases. The most commonly isolated viruses are adenovirus, cytomegalovirus (CMV), enteroviruses, herpes simplex virus (HSV), and varicella-zoster virus (VZV). Many viral infections (eg, HSV, CMV, VZV) can now be treated with antiviral drugs. Early laboratory diagnosis by isolation is very helpful in the medical management of these patients. Viruses that are detected in cell culture include: adenovirus, CMV, enterovirus, HSV, and VZV. Viruses that are not detected in cell culture include: Epstein-Barr virus, rubella virus (must order serology), West Nile virus, human papillomavirus, Norwalk virus or norovirus.

**Useful For:** Diagnosing viral infections in nonrespiratory specimens

**Interpretation:** A positive result indicates that virus was present in the specimen submitted. Clinical correlation is necessary to determine the significance of this finding. Negative results may be seen in a number of situations including absence of viral disease, inability of the virus to grow in culture (examples of organisms not detected by this culture test include Epstein-Barr virus, rubella virus, papilloma, and Norwalk virus), and nonviable organisms submitted. For patients with diarrhea, see Parasitic Investigation of Stool Specimens Algorithm in Special Instructions for other diagnostic tests that may be useful.

**Reference Values:**
Negative
If positive, virus is identified.

**Clinical References:**

**VRESP**
88926

**Viral Culture, Respiratory**

**Clinical Information:** Viruses are responsible for a broad spectrum of clinical symptoms and diseases. The most commonly isolated viruses are adenovirus, cytomegalovirus (CMV), enteroviruses, herpes simplex virus (HSV), influenza virus, parainfluenza virus (types 1-3), respiratory syncytial virus (RSV), and varicella-zoster virus (VZV). Many viral infections can now be treated with antiviral drugs. Early laboratory diagnosis by isolation is very helpful in the medical management of these patients. Viruses that are detected in cell culture: adenovirus, CMV, enterovirus, HSV, VZV, RSV, influenza
virus, and parainfluenza virus. Viruses that are not detected in cell culture: Epstein-Barr virus, rubella virus (must order serology), and human papillomavirus, Norwalk or norovirus.

**Useful For:** Diagnosing viral infections in respiratory specimens

**Interpretation:** A positive result indicates that virus was present in the specimen submitted. Clinical correlation is necessary to determine the significance of this finding. Influenza virus infection is a state-mandated reportable disease. Negative results may be seen in a number of situations including absence of viral disease, inability of the virus to grow in culture (examples of organisms not detected by culture include Epstein-Barr virus, rubella virus, and papilloma virus), and nonviable organisms submitted. Parainfluenza virus type 4 also may not be detected by viral culture.

**Reference Values:**
Negative
If positive, virus is identified.

**Clinical References:**

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**Viscosity, Serum**

**Clinical Information:** Viscosity is the property of fluids to resist flow. Hyperviscosity may be manifested by oronasal bleeding, blurred vision, headaches, dizziness, nystagmus, deafness, diplopia, ataxia, paresthesias, or congestive heart failure. Funduscopic examination reveals dilation of retinal veins and flame shaped retinal hemorrhages. The most common cause of serum hyperviscosity is the presence of large concentrations of IgM monoclonal proteins, and Waldenstrom's macroglobulinemia accounts for 80% to 90% of hyperviscosity cases. Hyperviscosity syndrome can also occur in multiple myeloma patients. Because the ability of a monoclonal protein to cause hyperviscosity is affected by its concentration, molecular weight, and aggregation, sera with concentrations of monoclonal IgM >4 g/dL, IgA >5 g/dL, or IgG >6 g/dL, should be tested for hyperviscosity. Serum viscosity and electrophoresis are recommended before and after plasmapheresis in order to correlate viscosity and M-spike with patient symptoms. This correlation may be useful for anticipating the need for repeat plasmapheresis.

**Useful For:** Detection of increased viscosity Monitoring patients with hyperviscosity syndrome

**Interpretation:** Although viscosities >1.5 centipoises (cP) are abnormal, hyperviscosity is rarely present unless the viscosity is >3 cP.

**Reference Values:**
> or =16 years: < or =1.5 centipoises
Reference values have not been established for patients that are <16 years of age.


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**Vitamin A and Vitamin E, Serum**

**Clinical Information:** Vitamin A: The level of vitamin A in the plasma or serum is a reflection of the quantities of vitamin A and carotene ingested and absorbed by the intestine (carotene is converted to vitamin A by intestine absorptive cells and hepatocytes). Vitamin A plays an essential role in the function of the retina (adaptation to dim light), is necessary for growth and differentiation of epithelial tissue, and is required for growth of bone, reproduction, and embryonic development. Together with certain carotenoids, vitamin A enhances immune function, reducing the consequences of some infectious
diseases. Degenerative changes in eyes and skin are commonly observed in vitamin A deficiency. Poor adaptation of vision to darkness (night blindness) is an early symptom that may be followed by degenerative changes in the retina. In developing countries, vitamin A deficiency is the principal preventable cause of blindness. Severe or prolonged deficiency leads to dry eye (xerophthalmia) that can result in corneal ulcers, scarring, and blindness. Another important consequence of inadequate intake is acquired immunodeficiency disease, with an increased incidence of death related to infectious diseases. In patients with HIV, vitamin A deficiency is associated with increased disease progression and mortality. Vitamin A in excess can be toxic. In particular, chronic vitamin A intoxication is a concern in normal adults who ingest more than 15 mg per day, and in children who ingest more than 6 mg per day of vitamin A over a period of several months. Manifestations are various and include dry skin, cheilosis, glossitis, vomiting, alopecia, bone demineralization and pain, hypercalcemia, lymph node enlargement, hyperlipidemia, amenorrhea, and features of pseudotumor cerebri with increased intracranial pressure and papilledema. Liver fibrosis with portal hypertension and bone demineralization may also result. Congenital malformations, like spontaneous abortions, craniofacial abnormalities, and valvular heart disease have been described in pregnant women taking vitamin A in excess. Consequently, in pregnancy, the daily dose of vitamin A should not exceed 3 mg. Vitamin E (alpha-tocopherol): Vitamin E contributes to the normal maintenance of biomembranes, the vascular system, and the nervous systems, and provides antioxidant protection for vitamin A. The level of vitamin E in the blood plasma or serum after a 12- to 14-hour fast reflects the individual’s reserve status. The current understanding of the specific actions of vitamin E is very incomplete. The tocopherols (vitamin E and related fat-soluble compounds) function as antioxidants and free-radical scavengers, protecting the integrity of unsaturated lipids in the biomembranes of all cells and preserving retinol from oxidative destruction. Vitamin E is known to promote the formation of prostacyclin in endothelial cells and to inhibit the formation of thromboxanes in thrombocytes, thereby minimizing the aggregation of thrombocytes at the surface of the endothelium. Those influences on thrombocyte aggregation may be of significance in relation to risks for coronary atherosclerosis and thrombosis. Deficiency of vitamin E in children leads to reversible motor and sensory neuropathies; this problem also has been suspected in adults. Premature infants who require an oxygen-enriched atmosphere are at increased risk for bronchopulmonary dysplasia and retrolental fibroplasia. Supplementation with vitamin E has been shown to lessen the severity of, and may even prevent, those problems. In addition, low blood levels of vitamin E may be associated with abetalipoproteinemia, presumably as a result of a lack of the ability to form very low-density lipoproteins and chylomicrons in the intestinal absorptive cells of affected persons. Vitamin E toxicity has not been established clearly. Chronically excessive ingestion has been suspected as a cause of thrombophlebitis, although this has not been definitively verified. Deficiencies of vitamins A and E may arise from poor nutrition or from intestinal malabsorption. Persons at risk, especially children, include those with bowel disease, pancreatic disease, chronic cholestasis, celiac disease, cystic fibrosis, and intestinal lymphangiectasia. Infantile cholangiopathies that may lead to malabsorption of vitamins A and E include intrahepatic dysplasia and rubella-related embryopathy

**Useful For:** Diagnosing vitamin A deficiency and toxicity Evaluating persons with intestinal malabsorption of lipids Evaluating individuals with motor and sensory neuropathies for vitamin E deficiency Monitoring vitamin E status of premature infants requiring oxygenation

**Interpretation:** Vitamin A: The World Health Organization recommendations supplementation when vitamin A levels fall below 20.0 mcg/dL. Severe deficiency is indicated at levels less than 10.0 mcg/dL. Vitamin A values above 120.0 mcg/dL suggest hypervitaminosis A and associated toxicity. Vitamin E (alpha-tocopherol): -Values that indicate a need for supplementation: -Premature: <2.0 mg/L -Neonate: <2.0 mg/L -Child (3 months): <3.0 mg/L -Child (2 years): <3.0 mg/L -Adults: <3.0 mg/L Values that indicate significant excess: -Adults: >40.0 mg/L

**Reference Values:**

**VITAMIN A (RETINOL)**
- 0-6 years: 11.3-64.7 mcg/dL
- 7-12 years: 12.8-81.2 mcg/dL
- 13-17 years: 14.4-97.7 mcg/dL
- > or =18 years: 32.5-78.0 mcg/dL

**VITAMIN E (ALPHA-TOCOPHEROL)**
- 0-17 years: 3.8-18.4 mg/L
Vitamin A, Serum

Clinical Information: The level of vitamin A in the plasma or serum is a reflection of the quantities of vitamin A and carotene (provitamin A) ingested and absorbed by the intestine (carotene is converted to vitamin A by intestinal absorptive cells and hepatocytes). Vitamin A plays an essential role in the function of the retina (adaptation to dim light), is necessary for growth and differentiation of epithelial tissue, and is required for growth of bone, reproduction, and embryonic development. Together with certain carotenoids, vitamin A enhances immune function, reducing the consequences of some infectious diseases. Degenerative changes in eyes and skin are commonly observed in vitamin A deficiency. Poor adaptation of vision to darkness (night blindness) is an early symptom that may be followed by degenerative changes in the retina. In developing countries, vitamin A deficiency is the principal preventable cause of blindness. Severe or prolonged deficiency leads to dry eye (xerophthalmia) that can result in corneal ulcers, scarring, and blindness. Another important consequence of inadequate intake is acquired immunodeficiency disease, where an increased incidence of death is associated with deficient vitamin A levels. Increased susceptibility is associated with vitamin A deficiency. In patients with HIV, vitamin A deficiency is associated with increased disease progression and mortality. Vitamin A in excess can be toxic. In particular, chronic vitamin A intoxication is a concern in normal adults who ingest more than 15 mg per day and children who ingest more than 6 mg per day of vitamin A over a period of several months. Manifestations are various and include dry skin, cheilosis, glossitis, vomiting, alopecia, bone demineralization and pain, hypercalcemia, lymph node enlargement, hyperlipidemia, amenorrhea, and features of pseudotumor cerebri with increased intracranial pressure and papilledema. Liver fibrosis with portal hypertension may also result. Congenital malformations, like spontaneous abortions, craniofacial abnormalities, and valvular heart disease have been described in pregnant women taking vitamin A in excess. Consequently, in pregnancy, the daily dose of vitamin A should not exceed 3 mg.

Useful For: Diagnosing vitamin A deficiency and toxicity Monitoring vitamin A therapy

Interpretation: The World Health Organization recommendations supplementation when vitamin A levels fall below 20.0 mcg/dL. Severe deficiency is indicated at levels less than 10.0 mcg/dL. Vitamin A values above 120.0 mcg/dL suggest hypervitaminosis A and associated toxicity.

Reference Values:
0-6 years: 11.3-64.7 mcg/dL
7-12 years: 12.8-81.2 mcg/dL
13-17 years: 14.4-97.7 mcg/dL
> or =18 years: 32.5-78.0 mcg/dL

absorption. The body uses its vitamin B12 stores very economically, reabsorbing vitamin B12 from the ileum and returning it to the liver; very little is excreted. Vitamin B12 deficiency may be due to lack of IF secretion by gastric mucosa (eg, gastrectomy, gastric atrophy) or intestinal malabsorption (eg, ileal resection, small intestinal diseases). Vitamin B12 deficiency frequently causes macrocytic anemia, glossitis, peripheral neuropathy, weakness, hyperreflexia, ataxia, loss of proprioception, poor coordination, and affective behavioral changes. These manifestations may occur in any combination; many patients have the neurologic defects without macrocytic anemia. Pernicious anemia is a macrocytic anemia caused by vitamin B12 deficiency that is due to a lack of IF secretion by gastric mucosa. Serum methylmalonic acid and homocysteine levels are also elevated in vitamin B12 deficiency states. Folate: The term folate refers to all derivatives of folic acid. For practical purposes, serum folate is almost entirely in the form of N-(5)-methyl tetrahydrofolate.(4) Approximately 20% of the folate absorbed daily is derived from dietary sources; the remainder is synthesized by intestinal microbiota. Serum folate levels typically fall within a few days after dietary folate intake is reduced and may be low in the presence of normal tissue stores. RBC folate levels are less subject to short-term dietary changes. Significant folate deficiency is characterized by macrocytosis and megaloblastic anemia. Lower than normal serum folate also has been reported in patients with neuropsychiatric disorders, in pregnant women whose fetuses have neural tube defects, and in women who have recently had spontaneous abortions.(5) Folate deficiency is most commonly due to insufficient dietary intake and is most frequently encountered in pregnant women or in alcoholics. Other causes of low serum folate concentration include: -Excessive utilization (eg, liver disease, hemolytic disorders, and malignancies) -Rare inborn errors of metabolism (eg, dihydrofolate reductase deficiency, formiminotransferase deficiency, 5,10-methylenetetra-hydrofolate reductase deficiency, and tetrahydrofolate methyltransferase deficiency)

**Useful For:** Investigation of macrocytic anemia Workup of deficiencies seen in megaloblastic anemias Investigation of suspected folate deficiency

**Interpretation:** B12: Concentration of vitamin B12 <180 ng/L may cause megaloblastic anemia and/or peripheral neuropathies. Vitamin B12 concentrations <150 ng/L are considered evidence of vitamin B12 deficiency. Vitamin B12 concentrations between 150 ng/L and 300 ng/L are considered borderline. Follow-up testing for antibodies to intrinsic factor (IF) (IFBA / Intrinsic Factor Blocking Antibody, Serum) is recommended to identify this potential cause of vitamin B12 malabsorption. For specimens without antibodies, follow-up testing of vitamin B12 tissue deficiency by measuring methylmalonic acid (MMA) (MMAS / Methylmalonic Acid [MMA], Quantitative, Serum) and/or homocysteine (HCYSP / Homocysteine, Total, Plasma) may be indicated if the patient is symptomatic. A normal serum concentration of vitamin B12 does not rule out tissue deficiency of vitamin B12. The most sensitive test for vitamin B12 deficiency at the cellular level is the assay for MMA. If clinical symptoms suggest deficiency, measurement of MMA and homocysteine should be considered, even if serum vitamin B12 concentrations are normal. Folate: Serum folate is a relatively nonspecific test.(4) Low serum folate levels may be seen in the absence of deficiency and normal levels may be seen in patients with macrocytic anemia, dementia, neuropsychiatric disorders, and pregnancy disorders. Results <4 mcg/L are suggestive of folate deficiency. The cut-off is based on consensus and was derived from the US NHANES III data.(5) Evaluation of macrocytic anemias commonly requires measurement of the serum concentration of both vitamin B12 and folate; ideally they should be measured at the same point in time. Additional testing with homocysteine and MMA determinations may help distinguish between B12 and folate deficiency states. In folate deficiency, homocysteine levels are elevated and MMA levels are normal. In vitamin B12 deficiency, both homocysteine levels and MMA levels are elevated. See Vitamin B12 Deficiency Evaluation in Special Instructions.

**Reference Values:**

**VITAMIN B12**

180-914 ng/L

**FOLATE**

> or = 4.0 mcg/L

<4.0 mcg/L suggests folate deficiency

Vitamin B12 Assay, Serum

**Clinical Information:** Vitamin B12 (cobalamin) is necessary for hematopoiesis and normal neuronal function. In humans, it is obtained only from animal proteins and requires intrinsic factor (IF) for absorption. The body uses its vitamin B12 stores very economically, reabsorbing vitamin B12 from the ileum and returning it to the liver; very little is excreted. Vitamin B12 deficiency may be due to lack of IF secretion by gastric mucosa (eg, gastrectomy, gastric atrophy) or intestinal malabsorption (eg, ileal resection, small intestinal diseases). Vitamin B12 deficiency frequently causes macrocytic anemia, glossitis, peripheral neuropathy, weakness, hyperreflexia, ataxia, loss of proprioception, poor coordination, and affective behavioral changes. These manifestations may occur in any combination; many patients have the neurologic defects without macrocytic anemia. Pernicious anemia is a macrocytic anemia caused by vitamin B12 deficiency that is due to a lack of IF secretion by gastric mucosa. Serum methylmalonic acid and homocysteine levels are also elevated in vitamin B12 deficiency states.

**Useful For:** Investigation of macrocytic anemia Workup of deficiencies seen in megaloblastic anemias

**Interpretation:** A serum vitamin B12 level less than 180 ng/L may cause megaloblastic anemia and peripheral neuropathies. Vitamin B12 levels less than 150 ng/L is considered evidence of vitamin B12 deficiency. Follow-up with tests for antibodies to intrinsic factor (IFBA / Intrinsic Factor Blocking Antibody, Serum) are recommended to identify this potential cause of vitamin B12 malabsorption. For specimens without antibodies, follow-up testing of vitamin B12 tissue deficiency by measuring methylmalonic acid (MMA) (MMAS / Methylmalonic Acid [MMA], Quantitative, Serum) and/or homocysteine (HCYP / Homocysteine, Total, Plasma) may be indicated if the patient is symptomatic. Patients with serum B12 levels between 150 and 400 ng/L are considered borderline and should be evaluated further by functional tests for vitamin B12 deficiency. The plasma homocysteine level is a good screening test. A normal level effectively excludes vitamin B12 and folate deficiency in an asymptomatic patient. However, the test is not specific and many situations can cause an increased level. In contrast, an increased serum MMA level is more specific for cellular-level B12 deficiency and is not increased by folate deficiency. See Vitamin B12 Deficiency Evaluation in Special Instructions.

**Reference Values:**
180-914 ng/L

**Vitamin B3 Niacin in Plasma**

**Clinical Information:** The amino acid tryptophan can be metabolically converted into niacin. Vitamin B3, also called niacin and nicotinic acid, is a water soluble B vitamin. It plays a role in releasing energy from carbohydrates and fats, metabolizes proteins, and assists in the production of some hormones and in the formation of red blood cells. Niacin is also thought to prevent and treat diabetes, improve circulation (as inositol hexaniacinate); and relieve arthritis. Niacin deficiency causes pellagra. Other forms of niacin may help prevent the development of childhood diabetes (Type I) in high risk children. The beneficial use of niacin (nicotinic acid, but not niacinamide) to prevent or treat elevated blood lipids and reduce cardiovascular disease risk is documented. Large amounts of niacin may result in "niacin intolerance" in 15-40% of people who try it and the unpleasant side effect of "skin-flushing" (similar to hot flashes). The RDA for niacin is only 13-18 mg. Vitamin B3 has been used orally and intravenously in connection with various health conditions including: high triglycerides, dysmenorrhea, hypothyroidism, and multiple sclerosis.

**Reference Values:**
Units: ug/mL

**Adult Reference Range:**
- > or = 10 years
  - Normal: 0.50 - 8.45
  - Low: <0.50
  - High: >8.45

**Pediatric Reference Range:**
- <10 years
  - Normal: 0.50 - 8.91
  - Low: <0.50
  - High: >8.91

**Vitamin B5 (Pantothenic Acid) Bioassay**

**Reference Values:**

**Adult Reference Range**
- >10 Years: 37 - 147 ug/L

**Pediatric Reference Range**
- < or = 1 Year: 3.45 to 825 ug/L
- >1 year to 10 Years: 3.45 to 229.2 ug/L

**Vitamin B6 Profile (PLP and PA), Plasma**

**Clinical Information:** Vitamin B6 is a complex of 6 vitamers: pyridoxal, pyridoxol, pyridoxamine, and their 5’-phosphate esters. Due to its role as a cofactor in a number of enzymatic reactions, pyridoxal phosphate (PLP) has been determined to be the biologically active form of vitamin B6. Vitamin B6 deficiency is a potential cause of burning mouth syndrome and a possible potentiating factor for carpal tunnel and tarsal tunnel syndromes. Persons who present chronic, progressive nerve compression disorders may be deficient in vitamin B6 and should be evaluated. Vitamin B6 deficiency is associated with symptoms of scaling of the skin, severe gingivitis, irritability, weakness, depression, dizziness, peripheral neuropathy, and seizures. In the pediatric population, deficiencies have been characterized by diarrhea, anemia, and seizures. Markedly elevated PLP in conjunction with low levels of pyridoxic acid (PA) are observed in cases of hypophosphatasia, a disorder characterized by low levels of alkaline phosphatase and a range of skeletal abnormalities.

**Useful For:** Determining the overall success of a vitamin B6 supplementation program Diagnosis
Interpretation: Levels for fasting individuals falling in the range of 3 to 30 mcg/L for pyridoxic acid (PA) and 5 to 50 mcg/L for pyridoxal 5-phosphate (PLP) are indicative of adequate nutrition. The following are interpretative guidelines based upon PLP and PA results:

- If PLP is >100 mcg/L and PA is < or =30: The increased pyridoxal 5-phosphate is suggestive of hypophosphatasia. Consider analysis of serum alkaline phosphatase isoenzymes (ALKI / Alkaline Phosphatase, Total and Isoenzymes, Serum) and urinary phosphoethanolamine (AAPD / Amino Acids, Quantitative, Random, Urine).
- If PLP is >100 mcg/L and PA is 31 to 100 mcg/L or PLP is 81 to 100 mcg/L and PA is < or =30 mcg/L: The increased pyridoxal 5-phosphate is likely related to dietary supplementation; however a mild expression of hypophosphatasia cannot be excluded. Consider analysis of serum alkaline phosphatase isoenzymes (ALKI / Alkaline Phosphatase, Total and Isoenzymes, Serum) and urinary phosphoethanolamine (AAPD / Amino Acids, Quantitative, Random, Urine).
- If PLP is 51 to 80 mcg/L or PLP is 81 to 100 mcg/L and PA is >30 or PLP is >100 mcg/L and PA is >100 mcg/L: The elevated pyridoxal 5-phosphate is likely due to dietary supplementation.

Reference Values:

**PYRIDOXAL 5-PHOSPHATE**
- 5-50 mcg/L

**PYRIDOXIC ACID**
- 3-30 mcg/L

Clinical References:


**Vitamin B7, H (Biotin)**

Clinical Information: Biotin, vitamin B7, or vitamin H, is a water soluble vitamin. The vitamin plays a role in the transferring of carbon dioxide in the metabolism of fat, carbohydrate and protein by functioning as an enzyme cofactor. It is involved in multiple biochemical reactions including niacin metabolism, amino acid degradation, and the formation of purine, which is an integral part of nucleic acids. It interacts with histone by the action of biotinyl-transferase. Sometimes the vitamin is used in weight reduction programs. It may be prescribed as a supplement for diabetic patients due to its role in carbohydrate metabolism. Biotin is commonly found in vitamin B complex and many food sources, such as milk, yeast, egg yolk, cereal, and mushrooms. The reference daily intake [RDI of 101.9(c) (8) (IV)] for vitamin B7 is 300 micrograms. Deficiency in the vitamin may result in seborrheic dermatitis, alopecia, myalgia, hyperesthesia, and conjunctivitis. Disorders of biotin metabolism can be acquired or congenital. Biotinidase and holocarboxylase synthethase deficiency are the two better known forms of disorders. The lack of biotin-dependent pyruvate carboxylase, propionyl-CoA carboxylase, methylcrotonyl-CoA carboxylase, and acetyl-CoA carboxylase can lead to the life-threatening disorder of multiple carboxylase deficiency. Treatment involves a daily dose of approximately 10 mg biotin/day. Irreversible mental or neurological abnormalities may result from delayed clinical intervention.

Reference Values:

**Pediatric**<br> <12 yrs: 57.0 â€“ 2460.2 pg/mL<br> <br>**Adult**>or=12 yrs: 221.0 â€“ 3004.0 pg/mL

**Vitamin E, Serum**

Clinical Information: Vitamin E (alpha-tocopherol) contributes to the normal maintenance of biomembranes, the vascular system, and the nervous system, and provides antioxidant protection for vitamin A. The level of vitamin E in the plasma or serum after a 12- to 14-hour fast reflects the

Reference Values:
individual's reserve status. The current understanding of the specific actions of vitamin E is very incomplete. The tocopherols (vitamin E and related fat-soluble compounds) function as antioxidants and free-radical scavengers, protecting the integrity of unsaturated lipids in the biomembranes of all cells and preserving retinol from oxidative destruction. Vitamin E is known to promote the formation of prostacyclin in endothelial cells and to inhibit the formation of thromboxanes in thrombocytes, thereby minimizing the aggregation of thrombocytes at the surface of the endothelium. Those influences on thrombocyte aggregation may be of significance in relation to risks for coronary atherosclerosis and thrombosis. Deficiency of vitamin E in children leads to reversible motor and sensory neuropathies; this problem also has been suspected in adults. Premature infants who require an oxygen-enriched atmosphere are at increased risk for bronchopulmonary dysplasia and retrolental fibroplasia; supplementation with vitamin E has been shown to lessen the severity of, and may even prevent, those problems. Deficiencies of vitamin E may arise from poor nutrition or from intestinal malabsorption. At-risk persons, especially children, include those with bowel disease, pancreatic disease, chronic cholestasis, celiac disease, cystic fibrosis, and intestinal lymphangiectasia. Infantile cholangiopathies that may lead to malabsorption of vitamin E include intrahepatic and extrahepatic biliary atresia, paucity of intrahepatic bile ducts, arteriohepatic dysplasia, and rubella-related embryopathy. In addition, low blood levels of vitamin E may be associated with abetalipoproteinemia, presumably as a result of a lack of the ability to form very low-density lipoproteins and chylomicrons in the intestinal absorptive cells of affected persons. Vitamin E toxicity has not been established clearly. Chronically excessive ingestion has been implicated as a cause of thrombophlebitis, although this has not been definitively verified.

**Useful For:** Evaluation of individuals with motor and sensory neuropathies Monitoring vitamin E status of premature infants requiring oxygenation Evaluation of persons with intestinal malabsorption of lipids

**Interpretation:** Values that indicate a need for supplementation: -Premature: <2.0 mg/L -Neonate: <2.0 mg/L -Child (3 months): <3.0 mg/L -Child (2 years): <4.0 mg/L -Adult: <4.0 mg/L Values that indicate significant excess: -Adult: >40.0 mg/L

**Reference Values:**

- 0-17 years: 3.8-18.4 mg/L
- > or =18 years: 5.5-17.0 mg/L

Significant deficiency: <3.0 mg/L

Significant excess: >40 mg/L


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**Vitamin K1, Serum**

**Clinical Information:** Vitamin K1 or phylloquinone is part of a group of similar fat soluble vitamins in which the 2-methyl-1,4-naphthoquinone ring is common. Phylloquinone is found in high amounts in leafy green vegetables and some fruits (avocado, kiwi). It is a required cofactor involved in the gamma-carboxylation of glutamate residues of several proteins. Most notably, the inactive forms of the coagulation factors prothrombin (factor II), factors VII, IX, and X and protein S and protein C are converted to their active forms by the transformation of glutamate residues to gamma-carboxyglutamic acid (Gla). Other proteins such as those involved in bone metabolism, cell growth, and apoptosis also undergo this Gla transformation. Measurement of vitamin K1 (phyloquinone) in fasting serum is a strong indicator of dietary intake and status.

**Useful For:** Assessment of circulating vitamin K1 concentration

**Interpretation:** Low vitamin K1 concentrations in the serum are indicative of insufficiency and poor vitamin K1 status.

**Reference Values:**

- > or =18 years: 0.10-2.20 ng/mL
<18 years: not established


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**VLTB**

**89190**

**Volatile Screen, Blood**

**Clinical Information:** Volatile substances in the blood include ethanol, methanol, isopropanol, and acetone. Acetone is generally elevated in metabolic conditions such as diabetic ketoacidosis. Methanol and isopropanol are highly toxic and result from exogenous ingestion. Ethanol is the single most important substance of abuse in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. Ethanol acts on cerebral function as a depressant similar to general anesthetics. This depression causes most of the typical symptoms such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment progressively increases. In most jurisdictions in the United States, the per se blood level for being under the influence of alcohol (ethanol) for purposes of driving a motor vehicle is 80 mg/dL.

**Useful For:** Detection and quantitation of acetone, methanol, isopropanol, and ethanol in whole blood

Quantification of the concentration of ethanol in blood that correlates with the degree of intoxication

Evaluation of toxicity to the measured volatile substances

**Interpretation:** Methanol: The presence of methanol indicates exposure which may result in intoxication, central nervous system (CNS) depression, and metabolic acidosis. Ingestion of methanol can be fatal if patients do not receive immediate medical treatment. Ethanol: The presence of ethanol indicates exposure which may result in intoxication, CNS depression, and metabolic acidosis. Isopropanol: The presence of isopropanol indicates exposure which may result in intoxication and CNS depression. Ingestion of isopropanol can be fatal if patients do not receive immediate medical treatment. Acetone: The presence of acetone may indicate exposure to acetone; it is also a metabolite of isopropanol and may be detected during ketoacidosis.

**Reference Values:**

**METHANOL**

Not detected (Positive results are quantitated.)

Toxic concentration: > or =10 mg/dL

**ETHANOL**

Not detected (Positive results are quantitated.)

Toxic concentration: > or =400 mg/dL

**ISOPROPNAL**

Not detected (Positive results are quantitated.)

Toxic concentration: > or =10 mg/dL

**ACETONE**

Not detected (Positive results are quantitated.)

Toxic concentration: > or =10 mg/dL

**Volatile Screen, Chain of Custody, Blood**

**Clinical Information:** Volatile substances in the blood include ethanol, methanol, isopropanol, and acetone. Acetone is generally elevated in metabolic conditions such as diabetic ketoacidosis. Methanol and isopropanol are highly toxic and result from exogenous ingestion. Ethanol is the single most important substance of abuse in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. Ethanol acts on cerebral function as a depressant similar to general anesthetics. This depression causes most of the typical symptoms such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment progressively increases. In most jurisdictions in the United States, the per se blood level for being under the influence of alcohol (ethanol) for purposes of driving a motor vehicle is 80 mg/dL. Chain of custody is required whenever the results of testing could be used in a court of law. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** All testing is performed under strict chain of custody Detection and quantitation of acetone, methanol, isopropanol, and ethanol in whole blood Quantification of the concentration of ethanol in blood that correlates with the degree of intoxication Evaluation of toxicity to the measured volatile substances

**Interpretation:** Methanol: The presence of methanol indicates exposure which may result in intoxication, central nervous system (CNS) depression, and metabolic acidosis. Ingestion of methanol can be fatal if patients do not receive immediate medical treatment. Ethanol: The presence of ethanol indicates exposure which may result in intoxication, CNS depression, and metabolic acidosis. Isopropanol: The presence of isopropanol indicates exposure which may result in intoxication and CNS depression. Ingestion of isopropanol can be fatal if patients do not receive immediate medical treatment. Acetone: The presence of acetone may indicate exposure to acetone; it is also a metabolite of isopropanol and may be detected during ketoacidosis.

**Reference Values:**

**METHANOL**
- Not detected (Positive results are quantitated.)
- Toxic concentration: > or =10 mg/dL

**ETHANOL**
- Not detected (Positive results are quantitated.)
- Toxic concentration: > or =400 mg/dL

**ISOPROPANOL**
- Not detected (Positive results are quantitated.)
- Toxic concentration: > or =10 mg/dL

**ACETONE**
- Not detected (Positive results are quantitated.)
- Toxic concentration: > or =10 mg/dL

**Clinical References:**
**Clinical Information:** Urine provides a medium for easy screening for methanol, ethanol, isopropanol, and acetone. Chain of custody is a record of the disposition of a specimen to document who collected it, who handled it, and who performed the analysis. When a specimen is submitted in this manner, analysis will be performed in such a way that it will withstand regular court scrutiny.

**Useful For:** Detecting the presence of acetone, methanol, isopropanol, or ethanol in urine with subsequent quantitation. Chain of custody is required whenever the results of testing could be used in a court of law. Its purpose is to protect the rights of the individual contributing the specimen by demonstrating that it was under the control of personnel involved with testing the specimen at all times; this control implies that the opportunity for specimen tampering would be limited.

**Interpretation:** Methanol: The presence of methanol indicates exposure which may result in intoxication, central nervous system (CNS) depression, and metabolic acidosis. Ingestion of methanol can be fatal if patients do not receive immediate medical treatment. Ethanol: The presence of ethanol indicates exposure which may result in intoxication, CNS depression, and metabolic acidosis. Isopropanol: The presence of isopropanol indicates exposure which may result in intoxication and CNS depression. Ingestion of isopropanol can be fatal if patients do not receive immediate medical treatment. Acetone: The presence of acetone may indicate exposure to acetone; it is also a metabolite of isopropanol and may be detected during ketoacidosis.

**Reference Values:**

**METHANOL**
- Not detected (Positive results are quantitated.)
- Cutoff concentration: 10 mg/dL
- Toxic concentration: > or =10 mg/dL

**ETHANOL**
- Not detected (Positive results are quantitated.)
- Cutoff concentration: 10 mg/dL

**ISOPROPA NOL**
- Not detected (Positive results are quantitated.)
- Cutoff concentration: 10 mg/dL
- Toxic concentration: > or =10 mg/dL

**ACETONE**
- Not detected (Positive results are quantitated.)
- Cutoff concentration: 10 mg/dL
- Toxic concentration: > or =10 mg/dL


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**Volatile Screen, Serum**

**Clinical Information:** Volatile substances in the blood include ethanol, methanol, isopropanol, and acetone. -Ethanol is the single most important substance of abuse in the United States. It is the active agent in beer, wine, vodka, whiskey, rum, and other liquors. -Methanol and isopropanol are highly toxic; toxicity results from ingestion (exogenous). -Acetone is generally elevated in metabolic conditions such as diabetic ketoacidosis (endogenous). It also is a metabolite of isopropanol. Ethanol acts on cerebral function as a depressant similar to general anesthetics. This depression causes most of the typical symptoms such as impaired thought, clouded judgment, and changed behavior. As the level of alcohol increases, the degree of impairment progressively increases. On average, the serum or plasma concentration of the alcohols is 1.2-fold higher than blood concentration. For example, the serum or
plasma would contain approximately 0.10 g/dL of ethanol in a blood specimen that contains 0.08 g/dL ethanol. Due to potential variations in the serum to whole blood ratio, serum should not be used in a medico-legal context. However, in the context of medical/clinical assessment, serum or plasma may be submitted for analysis.

**Useful For:** Detection and quantitation of acetone, methanol, isopropanol, and ethanol in serum

Quantification of the concentration of ethanol in serum correlates with degree of intoxication Evaluation of toxicity to the measured volatile substances

**Interpretation:** Methanol: The presence of methanol indicates exposure which may result in intoxication, central nervous system (CNS) depression, and metabolic acidosis. Ingestion of methanol can be fatal if patients do not receive immediate medical treatment. Ethanol: The presence of ethanol indicates exposure which may result in intoxication, CNS depression, and metabolic acidosis. Isopropanol: The presence of isopropanol indicates exposure which may result in intoxication and CNS depression. Ingestion of isopropanol can be fatal if patients do not receive immediate medical treatment. Acetone: The presence of acetone may indicate exposure to acetone; it is also a metabolite of isopropanol and may be detected during ketoacidosis.

**Reference Values:**

**METHANOL**
- Not detected (Positive results are quantitated.)
- Toxic concentration: > or =10 mg/dL

**ETHANOL**
- Not detected (Positive results are quantitated.)
- Toxic concentration: > or =400 mg/dL

**ISOPROPANOL**
- Not detected (Positive results are quantitated.)
- Toxic concentration: > or =10 mg/dL

**ACETONE**
- Not detected (Positive results are quantitated.)
- Toxic concentration: > or =10 mg/dL

**Clinical References:**

**VLTU 8826**

**Volatile Screen, Urine**

**Clinical Information:** Urine provides a medium for easy screening for methanol, ethanol, isopropanol, and acetone.

**Useful For:** Detecting the presence of acetone, methanol, isopropanol, or ethanol in urine with subsequent quantitation

**Interpretation:** Methanol: The presence of methanol indicates exposure which may result in intoxication, central nervous system (CNS) depression, and metabolic acidosis. Ingestion of methanol can be fatal if patients do not receive immediate medical treatment. Ethanol: The presence of ethanol indicates exposure which may result in intoxication, CNS depression, and metabolic acidosis. Isopropanol: The presence of isopropanol indicates exposure which may result in intoxication and CNS depression. Ingestion of isopropanol can be fatal if patients do not receive immediate medical treatment. Acetone: The presence of acetone may indicate exposure to acetone; it is also a metabolite of isopropanol and may be detected during ketoacidosis.
Reference Values:
METHANOL
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL
Toxic concentration: > or =10 mg/dL

ETHANOL
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL

ISOPROPANOL
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL
Toxic concentration: > or =10 mg/dL

ACETONE
Not detected (Positive results are quantitated.)
Cutoff concentration: 10 mg/dL
Toxic concentration: > or =10 mg/dL

Clinical References: Unpublished Mayo information

VWD2N
von Willebrand Disease 2N (Subtype Normandy), Blood

Clinical Information: Hemophilia A (HA) and von Willebrand disease (VWD) are bleeding disorders caused by quantitative or qualitative defects in factor VIII (FVIII) or von Willebrand factor (VWF), respectively, and constitute 2 of the most common bleeding disorders. Hemophilia A is inherited as an X-linked recessive disorder while most subtypes of VWD are inherited as autosomal dominant disorders. VWF plays 2 essential roles in hemostasis. VWF mediates platelet adhesion to damaged blood vessel walls and VWF is a carrier protein for FVIII. Noncovalent binding of FVIII to VWF is necessary for normal survival of FVIII in the blood circulation. In patients with severe VWD, the circulating half-life of endogenous or infused FVIII is shortened. Mutations within the VWF gene regions encoding for the FVIII binding domain of VWF may produce a phenotype of isolated FVIII "deficiency" associated with a clinically mild-to-moderate bleeding disorder which may be misdiagnosed as HA. This mild VWD phenotype was first described in patients from the Normandy region of France, VWD Normandy (VWD Type 2N). VWD Type 2N inheritance pattern is autosomal recessive. In an international survey, VWD Normandy was detected in 58 (4.8%) of 1,198 patients previously diagnosed as having mild hemophilia A. Three VWF gene mutations (VWF Thr791Met, Arg816Trp, and Arg854Gln) accounted for 96% of patients with mutations in the FVIII binding domain of VWF.(3) Patients who are homozygous for 1 of the 3 common mutations have reduced levels of FVIII activity, whereas patients who are heterozygous typically have normal FVIII activity. However, patients who are heterozygous for 1 of the 3 common VWD Type 2N mutations may have decreased FVIII activity in the presence of a second (compound heterozygous) mutation in the VWF gene that typically results in a Type 1 or Type 3 VWD (quantitative defect). VWD Type 2N also has been associated with a more severe bleeding phenotype among patients who are homozygous for other mutations (VWF Glu24Lys) within the FVIII binding domain of VWF.(1,2) Additional studies suggest that 1.5% (3/199) to 13.8% (5/36) of patients with VWD Type 1 have a FVIII binding defect.(2,4) The diagnosis of VWD Type 2N is important for appropriate genetic counseling, because the inheritance of VWD Type 2N is autosomal recessive (as opposed to the X-linked recessive inheritance of HA). Optimal treatment or prophylaxis of bleeding requires products containing functional VWF.

Useful For: Diagnosis of von Willebrand disease (VWD) Type 2N Evaluation and genetic counseling of patients with mild-to-moderate hemophilia A with an atypical inheritance pattern Evaluation of hemophilia A patients with a shortened survival of infused factor VIII (FVIII) (not caused by a specific FVIII inhibitor) Evaluation of female patients with low FVIII activity and no prior family history of hemophilia A Evaluation of patients with Type 1 or Types 2A, 2B, or 2M VWD with FVIII activity discordantly-lower than the von Willebrand factor antigen level
**Interpretation:** Interpretive report will include specimen information, assay information, background information, and conclusions based on the test results. Clinical information and results of patient testing (factor VIII coagulant activity, von Willebrand factor antigen, and ristocetin cofactor activity) are useful for test interpretation.

**Reference Values:**
Negative

**Clinical References:**

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**Von Willebrand Factor Activity, Plasma**

**Clinical Information:** von Willebrand factor (VWF) is a multimeric adhesive glycoprotein that is important for platelet-platelet and platelet-vessel hemostatic interactions. In addition, plasma VWF serves as a carrier protein for coagulation factor VIII, stabilizing its procoagulant activity. VWF circulates in the blood in 2 distinct compartments, plasma VWF and platelet VWF. Plasma VWF mainly reflects VWF synthesis and release from vascular endothelial cells. Platelet VWF (about 10% of the blood VWF) reflects VWF synthesis by bone marrow megakaryocytes with storage primarily in the alpha granules of circulating platelets. VWF antigen measurement assesses the mass of plasma VWF protein, but does not measure platelet VWF protein. The major function of VWF (mediating platelet-platelet or platelet-vessel interaction) is most commonly assessed by measurement of plasma VWF activity. Patients with congenital severe type 3 von Willebrand disease (VWD) have markedly decreased or immeasurably low VWF antigen in the plasma (and in the platelets), and plasma VWF activity is very low or not detectable. Patients with types 2A and 2B variants of VWD (with abnormal plasma VWF function and multimeric structure) may have normal or decreased plasma VWF antigen, but typically have decreased plasma VWF activity, and decreased higher molecular weight VWF multimers in the plasma. Patients with type 2M or type 2N VWD have normal levels of antigen, but either decreased VWF activity not caused by absence of higher molecular weight VWF multimers (type 2M VWD), or decreased factor VIII coagulant activity (type 2N VWD). Patients with type 1 VWD (with decreased but normally functioning plasma VWF) have concordantly decreased plasma VWF antigen and activity. Patients with acquired von Willebrand syndrome (AVWS) may have either normal or decreased plasma VWF antigen, and decreased VWF activity. Note: This activity assay is most effective when it is combined with measurement of von Willebrand factor: VWF antigen and factor VIII coagulant activity, preferably as a panel of tests with reflexive testing and interpretive reporting [e.g. VWPR / von Willebrand Profile]).

**Useful For:** Diagnosis of von Willebrand disease (VWD) and differentiation of VWD subtypes or differentiation of VWD from hemophilia A Monitoring therapeutic efficacy of treatment with DDAVP (desmopressin) or VWF concentrates in patients with VWD

**Interpretation:** von Willebrand factor (VWF) activity is reduced in parallel with VWF antigen in von Willebrand disease (VWD), except in types 2A, 2B, and 2M, and some cases of acquired von Willebrand syndrome (AVWS) in which the VWF activity is disproportionately decreased relative to the level of VWF antigen. The VWF activity may be decreased in congenital VWD or AVWS that may be associated with are variety of disorders including monoclonal gammapathies, lymphoproliferative disorders, autoimmune disorders, hypothyroidism, severe aortic stenosis, left ventricular assist device, and arteriovenous malformation. The VWF activity may be increased in association with pregnancy or estrogen use (including oral contraceptives), acute ("acute-phase reactant") or chronic inflammation,
exercise or stress, liver disease, vasculitis, and thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS). Such increases in VWF activity may obscure the laboratory diagnosis of mild VWD.

**Reference Values:**

55-200%

Normal, full-term newborn infants may have mildly increased levels which reach adult levels by 90 days postnatal. Healthy, premature infants (30-36 weeks gestation) may have increased levels that reach adult levels by 180 days.

Note: Individuals of blood group "O" may have lower plasma von Willebrand factor (VWF) activity than those of other ABO blood groups, such that apparently normal individuals of blood group "O" may have plasma VWF activity as low as 40% to 50%, whereas the lower limit of the reference range for individuals of other blood groups may be 60% to 70%.

**Clinical References:**


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**VWAG 9051**

**von Willebrand Factor Antigen, Plasma**

**Clinical Information:** The von Willebrand factor (VWF) is a multimeric adhesive glycoprotein that is important for platelet-platelet and platelet-vessel hemostatic interactions. In addition, plasma VWF serves as a carrier protein for coagulation factor VIII, stabilizing its procoagulant activity. VWF circulates in the blood in 2 distinct compartments; plasma VWF mainly reflects VWF synthesis and release from vascular endothelial cells, and platelet VWF (about 10% of the blood VWF) reflects VWF synthesis by bone marrow megakaryocytes with storage primarily in the alpha granules of circulating platelets. VWF antigen measurement assesses the mass of plasma VWF protein, but does not reflect VWF functions or platelet VWF. The major function of VWF (mediating platelet-platelet or platelet-vessel interaction) is most commonly assessed by measurement of plasma ristocetin cofactor activity. Decreased VWF antigen may be seen in: -Congenital von Willebrand disease -Acquired VWD that may be associated with monoclonal gammopathies, lymphoproliferative disorders, autoimmune disorders, and hypothyroidism

Increased VWF antigen may be seen in association with: -Pregnancy and/or estrogen use -Inflammation (acute-phase reactant) -Exercise or stress -Liver disease -Vasculitis -Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome von Willebrand factor (VWF) antigen measurement is most effective when it is combined with measurement of VWF ristocetin cofactor activity and factor VIII coagulant activity, preferably as a panel of tests with reflexive testing and interpretive reporting. Within this context, VWF antigen measurement can be useful for: -Diagnosis of von Willebrand disease (VWD) and differentiation of VWD subtype -Differentiation of VWD from hemophilia A (in conjunction with factor VIII coagulant assay)

**Useful For:** Diagnosis of von Willebrand disease (VWD) and differentiation of VWD subtype (in conjunction with von Willebrand factor ristocetin cofactor activity and factor VIII coagulant activity)

Differentiation of VWD from hemophilia A (in conjunction with factor VIII coagulant assay) Monitoring therapeutic efficacy of treatment with DDAVP (desmopressin) or VWF concentrates in patients with VWD

**Interpretation:** von Willebrand factor (VWF) antigen assay results generally must be used together with assays of VWF ristocetin cofactor activity and factor VIII coagulant activity, for optimum clinical utility and diagnostic efficiency. The diagnosis of von Willebrand disease (VWD) requires a combination of clinical and laboratory information. We suggest ordering VWPR / von Willebrand Profile. Patients with congenital severe type III VWD have a markedly decreased or undetectable level of VWF antigen in the plasma (and in the platelets), in addition to a plasma ristocetin cofactor activity that is very low, or not
detectable. Patients with types IIA and IIB variants of VWF (with abnormal plasma VWF function and multimeric structure) may have normal or decreased plasma VWF antigen. However, they typically have decreased plasma ristocetin cofactor activity, along with decreased higher molecular-weight VWF multimers in the plasma. Patients with types IIM or IIN VWD have normal levels of VWF antigen. In spite of this, they either have decreased vWF ristocetin cofactor activity, not caused by absence of higher molecular weight vWF multimers (type IIM VWD), or decreased factor VIII coagulant activity (type IIN VWD). Patients with type I VWD (with decreased but normally functioning plasma VWF) have concordantly decreased plasma VWF antigen and ristocetin cofactor activity. Patients with acquired VWD may have either normal or decreased plasma VWF antigen.

**Reference Values:**
55-200%

Note: Individuals of blood group "O" may have lower plasma von Willebrand factor (VWF) antigen than other ABO blood groups, such that apparently normal individuals of blood group "O" may have plasma VWF antigen as low as 40% to 50%, whereas the lower limit of the reference range for individuals of other blood groups may be 60% to 70%.

Children: Neonates, infants, and children have normal or mildly increased plasma VWF antigen, with respect to the adult reference range.

**Clinical References:**

**VWF Factor Multimer Analysis, Plasma**

**Clinical Information:** von Willebrand factor (VWF) is a large multimeric plasma glycoprotein that has essential roles in primary hemostasis. Wild type VWF molecules are series of multimers varying in size from dimers to multimers over 40 subunits (>10 million Daltons). The largest multimers provide multiple binding sites that can interact with both platelet receptors and subendothelial matrix sites of injury, and are the most hemostatically active form of VWF. The biological functions of VWF are as follows: 1. VWF is a ligand and mediates platelet adhesion to the subendothelial collagen at the site of vessel wall injury by binding to the platelet receptor glycoprotein (GP)-Ib, V, IX complex and subendothelial collagen 2. VWF binds and stabilizes procoagulant factor VIII in the circulation 3. Under conditions of high shear, VWF also mediates platelet-platelet cohesion by binding to the platelet receptor GP-IIb/IIIa (integrin alpha IIb beta3) Von Willebrand disease (VWD) is the most common hereditary bleeding disorder that is caused by quantitative or qualitative VWF defect. VWD manifests clinically as easy bruising, mucocutaneous bleeding (eg, epistaxis, menorrhagia), and bleeding after trauma or surgery. VWD has been classified into 3 major types: -Type 1, typically an autosomal dominant disease, is the most common, accounting for approximately 70% of VWD patients. It represents a quantitative deficiency of VWF of variable severity. -Type 2, which is usually an autosomal dominant disease, is characterized by several qualitative abnormalities of VWF. Four subtypes have been identified: 2A, 2B, 2M, and 2N. -Type 3, an autosomal recessive disorder, leads to severe disease with virtually undetectable levels of VWF, as well as very low levels of factor VIII. Acquired von Willebrand syndrome (AVWS) is associated with a number of different disease states and is caused by several different pathophysiological mechanisms, including antibody formation, proteolysis, binding to tumor cells with increased clearance, and decreased synthesis. AVWS is most frequently described in patients with dysproteinemias (including monoclonal gammopathy of undetermined significance [MGUS], multiple myeloma, and macroglobulinemia), lymphoproliferative disorders, myeloproliferative disorders (eg, essential thrombocytopenia), autoimmune diseases (eg, systemic lupus erythematosus), high-shear stress cardiovascular conditions such as severe aortic stenosis, gastrointestinal angiodysplasia, and hypothyroidism.
Useful For: Subtyping of von Willebrand factor (VWF): -When results of complementary laboratory tests (e.g., F8A / Coagulation Factor VIII Activity Assay, Plasma; VWFX / von Willebrand Activity, Plasma; and VWAG / von Willebrand Factor Antigen, Plasma) are abnormally low or discordant.
-Primarily used to identify variants of type 2 VWF. -An aid in determining appropriate treatment

Interpretation: The plasma von Willebrand factor (VWF) multimer analysis is a qualitative visual assessment of the size spectrum and the banding pattern of VWF multimers. This test is used to identify variants of type 2 von Willebrand disease that have fewer of the largest multimers, have unusually large multimers, or have qualitatively abnormal "bands" that indicate an abnormal VWF structure.

Reference Values:
An interpretive report will be provided.

activity. Severe type 1 disease is also called type 3 VWD, but the distinction between the two may sometimes be difficult. Type 2 VWD: Type 2 VWD variants represent 20% to 30% of clinical VWD, typically autosomal dominant in inheritance. There are 4 subtypes of type 2 VWD: 2A, 2B, 2M, and 2N. Abnormal plasma HMW VWF function and multimeric structure with decreased or absent HMW multimers are characteristic of types 2A and 2B, but are normal in type 2M or 2N. VWF activity is decreased in types 2A, 2B, and 2M, and typically is discordantly lower than VWF antigen. Type 2N (Normandy) has substantially decreased factor VIII coagulant activity (typically 5%-30% of mean normal), with normal VWF antigen and activity and normal VWF multimers with clinical manifestation as autosomally inherited mild hemophilia (in contrast to classical X chromosome-linked hemophilia A). Type 2A is the most common of the 4. Type 2B manifests thrombocytopenia, either persistent or transient, and is distinguished from type 2A by abnormally heightened aggregation response of patient platelets and plasma to low dose ristocetin stimulation. Type 2M typically demonstrates hypofunctional VWF with decreased VWF activity discordantly lower than VWF antigen not due to loss of HMW multimers. One variant of type 2M, Vicenza variant VWD, has ultralarge VWF multimers in plasma. Type 3 VWD: VWF is absent or markedly decreased in type 3 VWD (VWF antigen and activity either undetectably low or below 5% to 10% of mean normal, with secondary decrease of factor VIII coagulant activity (5%-30%). VWF multimers may be undetectable or, if present, have a normal distribution. Platelet VWF may also be absent. Acquired VWD: VWD can also occur on an acquired basis by a variety of mechanisms not well understood. Disorders associated with acquired VWD include certain myeloproliferative or lymphoproliferative disorders, plasma cell dyscrasias including monoclonal gammopathy of undetermined significance, autoimmune disorders (eg, rheumatoid arthritis, systemic lupus erythematosus), and a variety of other diseases. In some cases, no associated disorder is detected. Laboratory testing currently cannot distinguish between congenital and acquired VWD; clinical correlation is required.

**Useful For:** Detection of deficiency or abnormality of von Willebrand factor (VWF) and related deficiency of factor VIII coagulant activity Subtyping von Willebrand disease (VWD) as type 1 (most common), type 2 variants (less common), or type 3 (rare) This test is not useful for detection of hemophilia carriers.

**Interpretation:** An interpretive report will be provided when testing is complete.

**Reference Values:**

**FACTOR VIII ACTIVITY**

55-200%

**von WILLEBRAND FACTOR ACTIVITY**

55-200%

**von WILLEBRAND FACTOR ANTIGEN**

55-200%


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**Voriconazole, Serum**

**Clinical Information:** Voriconazole (Vfend) is an antifungal agent approved for treatment of invasive aspergillosis and candidemia/candidiasis, as well as for salvage therapy for infections in patients refractory to or intolerant of other antifungal therapy. The drug inhibits the fungal enzyme 14α-sterol demethylase, a critical step in ergosterol biosynthesis. Voriconazole is metabolized in the liver primarily by CYP2C19; CYP2C9 and CYP3A4 play limited roles. The primary metabolite is voriconazole N-oxide, which has no antifungal activity. Drug clearance is primarily dependent on hepatic metabolism. The pharmacokinetics of voriconazole is highly variable and nonlinear, which results in an increased dose leading to a greater than proportional increase in serum concentration. The bioavailability of oral voriconazole is greater than 95%. Approximately 60% of the drug in serum is
protein bound. Voriconazole has a volume of distribution of 4.6 L/kg. Most (80%) of the drug is excreted in the urine, exclusively as metabolites. Adverse effects of voriconazole include visual disturbances, skin rashes, and elevated liver enzyme levels.

**Useful For:** Monitoring trough levels of voriconazole is suggested in individuals with reduced liver function, individuals with CYP2C19 polymorphisms associated with poor metabolic function, patients taking other medications that affect CYP2C19 activity, and in patients experiencing potential toxicity. Monitoring trough levels may be reasonable in patients who are not responding optimally or have drug interactions that may decrease voriconazole levels, or to ensure adequate oral absorption.

**Interpretation:** Trough levels above 6 mcg/mL (and especially >10 mcg/mL) have been associated with toxicity in several reports. Trough levels below 1 mcg/mL have been associated with suboptimal response in several reports.

**Reference Values:**
1.0-5.5 mcg/mL
Trough level (ie, immediately before next dose) monitoring is recommended.

**Clinical References:**

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**FWALP**

Wall Eyed Pike (Sander vitreus)(Stizostedion vitreum) IgE

**Interpretation:**

<table>
<thead>
<tr>
<th>Class IgE (kU/L)</th>
<th>Comment</th>
<th>Lower Limit of Quantitation</th>
<th>Upper Limit of Quantitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 &lt;0.10</td>
<td>Negative</td>
<td>0/1</td>
<td>0.10</td>
</tr>
<tr>
<td>0.10 – 0.34</td>
<td>Equivocal</td>
<td>0.35</td>
<td>0.69</td>
</tr>
<tr>
<td>0.69 – 0.70</td>
<td>Low Positive</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>0.70 – 3.4</td>
<td>Moderate Positive</td>
<td>3</td>
<td>3.5</td>
</tr>
<tr>
<td>3.5 – 17.4</td>
<td>High Positive</td>
<td>4</td>
<td>17.5</td>
</tr>
<tr>
<td>17.5 – 49.9</td>
<td>Very High Positive</td>
<td>49.9</td>
<td>99.9</td>
</tr>
<tr>
<td>99.9 – 100</td>
<td>Very High Positive</td>
<td>&gt;100</td>
<td></td>
</tr>
</tbody>
</table>

**Reference Values:**

<0.35 kU/L

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**FWALG**

Walnut Food (Juglans spp) IgG

**Interpretation:**

mcg/mL of IgG

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**WALN**

Walnut Tree, IgE

**Clinical Information:**

Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the
immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

Reference values apply to all ages.


**Walnut-Food, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
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<td>0.70-3.49</td>
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<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


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**Warfarin Response Genotype**

**Clinical Information:** Warfarin is a Coumarin-based drug commonly utilized in anticoagulation therapy to prevent thrombosis due to inherited and acquired hemostatic disorders. The drug is also used in a number of other medical conditions and treatments including atrial fibrillation and hip replacement surgery. Warfarin acts by interfering with the metabolism of vitamin K, which is necessary for production of key coagulation factors. Warfarin inhibits vitamin K recycling by blocking its metabolism at the vitamin K-epoxide intermediate; thereby decreasing the amount of available vitamin K. Warfarin has a narrow therapeutic window; undermedicating increases the risk for thrombosis and overmedicating increases the risk for cerebrovascular accidents. Warfarin therapy has one of the highest rates of severe adverse drug reactions. Warfarin is dosed using nongenetic factors including gender, weight, and age, and is monitored by coagulation testing in order to maintain the international normalized ratio (INR) within specific limits. However, warfarin metabolism is highly variable and dependent upon genetic factors. Variants within 3 genes and 1 intragenic locus are known to affect the metabolism of warfarin and the dose needed to maintain the correct serum drug level and degree of anticoagulation. The CYP2C9 gene encodes the cytochrome P450 2C9 (CYP2C9) enzyme that primarily metabolizes the more active isomer of warfarin (S-warfarin) to inactive products. Some CYP2C9 variants result in decreased enzymatic activity and may lead to increases in serum warfarin and over-medicating, driving the INR above the therapeutic target. The second gene (VKORC1) encodes vitamin K epoxide reductase complex subunit-1 (VKORC1), a small transmembrane protein of the endoplasmic reticulum that is part of the vitamin K cycle and the target of warfarin therapy. (1) Vitamin K epoxide, a by-product of the carboxylation of blood coagulation factors, is reduced to vitamin K by VKORC1. A VKORC1 promoter variant leads to decreased expression of the gene, resulting in reduced availability of vitamin K. This may cause increases in serum warfarin and overmedicating, driving the INR above the therapeutic target. In addition, there are variations in VKORC1 that lead to warfarin resistance that are tested by this assay. These variations are rare. CYP4F2 metabolizes reduced vitamin K to hydroxyl-vitamin K1, thus removing it from the pathways involved in the activation of clotting factors impacted by warfarin. In individuals who self-identify as being of non-African ancestry, carriers of the CYP4F2*3 (C.1297G->A; rs2108622) variant may need a small (5%-10%) warfarin dosage increase to achieve therapeutic goals. The rs12777823G->A variant is located intragenic in the CYP2C locus on chromosome 10. The A allele has been associated with the need for a 10% to 15% decrease in dose in individuals who self-identify as being of African ancestry. CYP2C9: CYP2C9 metabolizes a wide variety of drugs including warfarin and...
phenytoin. (Note that if testing is desired for other CYP2C9 substrates, order 2C9GV / Cytochrome P450 2C9 Genotype. A number of specific CYP2C9 variants result in enzymatic deficiencies. The following information outlines the relationship between the variants detected in this assay and their effect on the activity of the enzyme (Table 1): Table 1: CYP2C9 Allele cDNA Nucleotide Change Effect on Enzyme Metabolism *1 None (wild type) Normal activity *2 430C->T Reduced activity *3 1075A->C No activity *4 1076T->C Reduced activity *5 1080C->G Reduced activity *6 818delA No activity *8 449G->A Substrate specific *9 752A->G Reduced activity *11 1003C->T Reduced activity *12 1465C->T Reduced activity *13 269C->T Minimal activity *14 374G->T No activity *15 389C->G No activity *16 895A->G Minimal activity *17 1144C->T Reduced activity *18 1190A->C No activity *25 253_362del No activity *26 389C->G Minimal activity *28 641A->T Minimal activity *30 1429G->A Minimal activity *33 395G->A Minimal activity *35 374G->T + 430C->T No activity VKORC1: The c.-1639 promoter variant is located in the second nucleotide of an E-Box (CANNTG) and its presence disrupts the consensus sequence, reducing promoter activity. In vitro experiments show a 44% higher transcription level of the G versus the A allele.(1) The c.-1639 G->A nucleotide change results in decreased gene expression and reduced enzyme activity. This test also determines the genotype for multiple other loci within VKORC1 that have been associated with warfarin resistance. The mechanism by which these variations cause warfarin resistance is not clearly understood. Table 2: Additional Variants Tested Gene/SNV cDNA Nucleotide Change Effect on Enzyme Metabolism VKORC1 -1639G->A Warfarin sensitivity VKORC1 85G->T Warfarin resistance VKORC1 106G->T Warfarin resistance VKORC1 121G->T Warfarin resistance VKORC1 134T->C Warfarin resistance VKORC1 172A->G Warfarin resistance VKORC1 196G->A Warfarin resistance VKORC1 358C->T Warfarin resistance VKORC1 383T->G Warfarin resistance CYP4F2*3 1297G->A Warfarin resistance rs12777823G->A(a) Warfarin sensitivity a. rs12777823G->A is an intergenic single nucleotide variant (SNV) Warfarin dosing may require adjustment depending on the genotypes identified and the predicted phenotype. Patients who have high warfarin sensitivity may benefit from greatly reduced warfarin dosage or by transitioning to another comparable medication.(2) Similarly, in rare instances, individuals with VKORC1 warfarin resistance variants, may require a higher warfarin dose or may benefit from selection of an alternate medication.

**Useful For:** Identifying patients who may require warfarin dosing adjustments(3,4) including:
- Patients being started on a first prescription for warfarin
- Patients who have previously been prescribed warfarin and have required multiple dosing adjustments to maintain the international normalized ratio in the target range
- Patients with a history of thrombosis or bleeding when taking warfarin

**Interpretation:** An interpretive report will be provided that includes assay information, genotype, and an interpretation indicating the patient's predicted warfarin response. The CYP2C9 and CYP4F2 genotypes, with associated star alleles, are assigned using standard allelic nomenclature as published by the Pharmacogene Variation (PharmVar) Consortium.(5) Individuals without a detectable alteration in CYP2C9 or CYP4F2 will be designated as CYP2C9*1/*1 or CYP4F2*1/*1 For additional information regarding pharmacogenomic genes and their associated drugs, see Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices. Individuals who have variants in 1 or more gene tested by this assay may require more frequent monitoring of international normalized ratio (INR) to maintain the INR in the target range. Drug-drug interactions and drug/metabolite inhibition must be considered when prescribing warfarin. Warfarin metabolism may be inhibited through drug-drug interactions, including amiodarone and some statins. It is important to interpret the results of testing and dose adjustments in the context of hepatic and renal function and patient age.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Warfarin, Serum**

**Clinical Information:** Warfarin (Coumadin) is an anticoagulant that acts by antagonizing the action of vitamin K resulting in the same coagulation abnormalities produced by vitamin K deficiency. Warfarin reduces the levels of prothrombin and factors VII, IX, and X, thereby prolonging the prothrombin and partial thromboplastin times. Warfarin produces its anticoagulant effect within 36 to 72 hours of initiating therapy, and the duration of action may persist for 4 to 5 days following withdrawal of drug. Warfarin circulates almost completely bound to albumin (>98%), and its half-life ranges from 20 to 60 hours. Abnormal bleeding is the chief complication of overdose.

**Useful For:** Monitoring patients whose prothrombin time is inconsistent with the prescribed warfarin dose, particularly when failure to comply or surreptitious drug use is suspected. Note: This test is not useful for evaluation of the patient with prolonged bleeding time suspected of exposure to rat poisons.

**Interpretation:** Therapeutic concentration: 2.0 to 5.0 mcg/mL Toxic concentration: > or =10.0 mcg/mL

**Reference Values:**
Therapeutic concentration: 2.0-5.0 mcg/mL
Toxic concentration: > or =10.0 mcg/mL


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**Wasp Venom, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.
**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.


**Watermelon IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

**Watermelon, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity
of allergic reactions to insect venom allergens, drugs, or chemical allergens

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**WEED1 Weed Panel # 1**

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**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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**West Nile CSF Interpretation**

**Clinical Information:** West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds but can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe.(1-3) Most recently, in 2012, a total of 5,674 cases of WNV were reported to the CDC, among which 2,873 (51%) were classified as neuroinvasive disease (eg, meningitis or encephalitis) and 286 (5%) cases resulted in death.(2) Most people who are infected with WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk.(1) Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. PCR (LCWNV / West Nile Virus, Molecular Detection, PCR) can detect WNV RNA in specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in cerebrospinal fluid and approximately 10% in blood, from patients with known WNV infection.

**Useful For:** Only orderable as part of a profile. See WNC / West Nile Virus Antibody, IgG and IgM, Spinal Fluid. Aids in diagnosis of central nervous system infection with West Nile virus.

**Interpretation:** IgM: A positive result is consistent with the acute phase of West Nile virus (WNV) meningitis or encephalitis. In the very early stages of acute WNV infection, IgM may be detectable in
cerebrospinal fluid (CSF) before it becomes detectable in serum. A negative result may indicate absence of disease. However, specimens drawn too early in the acute phase may be negative for IgM-class antibodies to WNV. If WNV central nervous system infection is suspected, a second specimen should be collected in 1 to 2 weeks and tested. IgG: A positive result may indicate recent or past central nervous system (CNS) infection with WNV. Clinical correlation is necessary. This assay is unable to distinguish between intrathecal antibody synthesis and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. Positive results should be interpreted with other laboratory and clinical data prior to a diagnosis of CNS infection.

Reference Values:
Only orderable as part of a profile. See WNC / West Nile Virus Antibody, IgG and IgM, Spinal Fluid.

Reference Values:
Only orderable as part of a profile. For more information see WNS / West Nile Virus Antibody, IgG and IgM, Serum.

Clinical References:

WNVP
87802

West Nile Virus (WNV), Molecular Detection, PCR, Plasma

Clinical Information:
West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA virus) that primarily infects birds but can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe.(1-3) Most people who are infected with WNV do not experience symptoms. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms including headache, myalgia, and occasionally a skin rash on the trunk of the body. About 1 of 150 WNV infections (<1%) result in meningitis or encephalitis. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk. Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum or cerebrospinal fluid (CSF) specimens (WNV / West Nile Virus [WNV] Antibody, IgG and IgM, Serum or WNVC / West Nile Virus [WNV] Antibody, IgG and IgM, Spinal Fluid). The specific identification of WNV by detection of IgM in CSF is the recommended test to document central nervous system disease, but this test may be falsely negative in CSF collected <8 days after the onset of symptoms. Alternatively, experiences in nucleic acid testing for WNV RNA in blood prior to transfusion have indicated that PCR can detect viremic target RNA from patients with known West Nile infection when specific antibodies to the virus are not present (ie, from 2-8 days after onset of symptoms).(4,5)

Useful For: Rapid testing for West Nile virus (WNV) RNA As an adjunct in the diagnosis of early WNV virus infection

Interpretation: The likelihood of detection of West Nile virus RNA by PCR is relatively low. In cerebrospinal fluid, the clinical sensitivity is approximately 55%, and in blood, about 10%. Specificity of the assay in either matrix is approximately 100%.(6)

Reference Values:
Negative

WNS
36769

West Nile Virus Antibody, IgG and IgM, Serum

Clinical Information:
West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds but can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe.(1-3) Most recently, in 2012, a total of 5,674 cases of WNV were reported to the Centers for Disease Control and Prevention (CDC), among which 2,873 (51%) were classified as neuroinvasive disease (eg, meningitis or encephalitis) and 286 (5%) cases resulted in death.(2) Most people who are infected with WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of
the body. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk.(1) Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. PCR (WNVP / West Nile Virus (WNV), Molecular Detection, PCR, Plasma) can detect WNV RNA in plasma specimens from patients with recent WNV infection (ie, 3 to 5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in cerebrospinal fluid and approximately 10% in blood, from patients with known WNV infection.

Useful For: Laboratory diagnosis of infection with West Nile virus in serum specimens

Interpretation: IgG: The presence of IgG-class antibodies to West Nile virus (WNV) in serum indicates infection with WNV at some time in the past. By 3 weeks postinfection, virtually all infected persons should have developed IgG antibodies to WNV. If acute-phase infection is suspected, serum specimens drawn within approximately 7 days postinfection should be compared with a specimen drawn approximately 14 to 21 days postinfection to demonstrate rising IgG antibody levels between the 2 serum specimens. IgM: Presence of specific IgM-class antibodies in a serum specimen is consistent with acute-phase infection with WNV. By the 8th day of illness, most infected persons will have detectable serum IgM antibody to WNV; in most cases it will be detectable for at least 1 to 2 months following disease resolution and in some cases will be detectable for 12 months or longer. The absence of IgM antibodies to WNV is consistent with lack of acute-phase infection with this virus. Specimens drawn too early in the acute phase (eg, before 8 to 10 days postinfection) may be negative for IgM-specific antibodies to WNV. If WNV is suspected, a second specimen drawn approximately 14 days postinfection should be tested. In the very early stages of WNV infection, IgM may be detectable in cerebrospinal fluid (CSF) before it becomes detectable in serum.

Reference Values:
IgG: negative
IgM: negative

approximately 55% in cerebrospinal fluid and approximately 10% in blood, from patients with known WNV infection.

**Useful For:** Aids in diagnosis of central nervous system infection with West Nile virus

**Interpretation:**
- **IgM:** A positive result is consistent with the acute phase of West Nile virus (WNV) meningoencephalitis. In the very early stages of acute WNV infection, IgM may be detectable in cerebrospinal fluid (CSF) before it becomes detectable in serum. A negative result may indicate absence of disease. However, specimens drawn too early in the acute phase may be negative for IgM-class antibodies to WNV. If WNV central nervous system infection is suspected, a second specimen should be collected in 1 to 2 weeks and tested.
- **IgG:** A positive result may indicate recent or past central nervous system (CNS) infection with WNV. Clinical correlation is necessary. This assay is unable to distinguish between intrathecal antibody synthesis and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. Positive results should be interpreted with other laboratory and clinical data prior to a diagnosis of CNS infection.

**Reference Values:**
- IgG: Negative
- IgM: Negative

Reference values apply to all ages.

**Clinical References:**

**West Nile Virus Antibody, IgG, Serum**

**Clinical Information:** West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds but can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe.(1-3) Most recently, in 2012, a total of 5,674 cases of WNV were reported to the Centers for Disease Control and Prevention (CDC), among which 2,873 (51%) were classified as neuroinvasive disease (eg, meningitis or encephalitis) and 286 (5%) cases resulted in death.(2) Most people who are infected with WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk.(1) Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. PCR (WNVP / West Nile Virus (WNV), Molecular Detection, PCR, Plasma) can detect WNV RNA in plasma specimens from patients with recent WNV infection (ie, 3 to 5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in cerebrospinal fluid and approximately 10% in blood, from patients with known WNV infection.

**Useful For:** Laboratory diagnosis of infection with West Nile virus

**Interpretation:**
- **IgG:** The presence of IgG-class antibodies to West Nile virus (WNV) in serum indicates infection with WNV at some time in the past. By 3 weeks postinfection, virtually all infected persons should have developed IgG antibodies to WNV. If acute-phase infection is suspected, serum specimens drawn within approximately 7 days postinfection should be compared with a specimen
drawn approximately 14 to 21 days after infection to demonstrate rising IgG antibody levels between
the 2 serum specimens. IgM: Presence of specific IgM-class antibodies in a serum specimen is
consistent with acute-phase infection with WNV. By the 8th day of illness, most infected persons will
have detectable serum IgM antibody to WNV; in most cases it will be detectable for at least 1 to 2
months following disease resolution and in some cases will be detectable for 12 months or longer. The
absence of IgM antibodies to WNV is consistent with lack of acute-phase infection with this virus.
Specimens drawn too early in the acute phase (eg, before 8 to 10 days post-infection) may be negative
for IgM-specific antibodies to WNV. If WNV is suspected, a second specimen drawn approximately 14
days postinfection should be tested. In the very early stages of WNV infection, IgM may be detectable
cerebrospinal fluid (CSF) before it becomes detectable in serum.

Reference Values:
Only orderable as part of a profile. For more information see WNS / West Nile Virus Antibody, IgG and
IgM, Serum.

Clinical References: 
Intern Med 2002;137:173-179 2. MMWR: West Nile Virus and Other Arboviral Diseases-United States,
and Prevention (CDC). Provisional Surveillance Summary of the West Nile Virus epidemic. United
Disease Control and Prevention (CDC). Investigations of West Nile Virus infections in recipients of blood
transfusions. MMWR Morb Mortal Wkly Rep 2002;51(43):973-974

West Nile Virus Antibody, IgG, Spinal Fluid
Clinical Information: West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA)
that primarily infects birds but can also infect humans and horses. WNV was first isolated in 1937 from an
infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in
birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in
Africa, Asia, the Middle East, and Europe.(1-3) Most recently, in 2012, a total of 5,674 cases of WNV
were reported to the CDC, among which 2,873 (51%) were classified as neuroinvasive disease (eg,
meningitis or encephalitis) and 286 (5%) cases resulted in death.(2) Most people who are infected with
WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become
infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and
occasionally a skin rash on the trunk of the body. Case fatality rates among patients hospitalized during
recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death,
and patients older than 70 years of age are at particularly high risk.(1) Laboratory diagnosis is best
achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. PCR (LCWNV /
West Nile Virus, Molecular Detection, PCR) can detect WNV RNA in specimens from patients with
recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet
present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is
approximately 55% in cerebrospinal fluid and approximately 10% in blood, from patients with known
WNV infection.

Useful For: Only orderable as part of a profile. See WNC / West Nile Virus Antibody, IgG and IgM,
Spinal Fluid. Aids in diagnosis of central nervous system infection with West Nile virus

Interpretation: A positive result may indicate recent or past central nervous system (CNS) infection
with West Nile virus (WNV). Clinical correlation is necessary. This assay is unable to distinguish
between intrathecal antibody synthesis and serum antibodies introduced into the cerebrospinal fluid at the
time of lumbar puncture or from a breakdown in the blood-brain barrier. Positive results should be
interpreted with other laboratory and clinical data prior to a diagnosis of CNS infection.

Reference Values:
Only orderable as part of a profile. See WNC / West Nile Virus Antibody, IgG and IgM, Spinal Fluid.

West Nile Virus Antibody, IgM, Serum

**Clinical Information:** West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds but can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe.(1-3) Most recently, in 2012, a total of 5,674 cases of WNV were reported to the Centers for Disease Control and Prevention (CDC), among which 2,873 (51%) were classified as neuroinvasive disease (e.g., meningitis or encephalitis) and 286 (5%) cases resulted in death.(2) Most people who are infected with WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk.(1) Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. PCR (WNVP / West Nile Virus (WNV), Molecular Detection, PCR, Plasma) can detect WNV RNA in plasma specimens from patients with recent WNV infection (i.e., 3 to 5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in cerebrospinal fluid and approximately 10% in blood, from patients with known WNV infection.

**Useful For:** Laboratory diagnosis of infection with West Nile virus

**Interpretation:** IgG: The presence of IgG-class antibodies to West Nile virus (WNV) in serum indicates infection with WNV at some time in the past. By 3 weeks postinfection, virtually all infected persons should have developed IgG antibodies to WNV. If acute-phase infection is suspected, serum specimens drawn within approximately 7 days postinfection should be compared with a specimen drawn approximately 14 to 21 days after infection to demonstrate rising IgG antibody levels between the 2 serum specimens. IgM: Presence of specific IgM-class antibodies in a serum specimen is consistent with acute-phase infection with WNV. By the 8th day of illness, most infected persons will have detectable serum IgM antibody to WNV; in most cases it will be detectable for at least 1 to 2 months following disease resolution and in some cases will be detectable for 12 months or longer. The absence of IgM antibodies to WNV is consistent with lack of acute-phase infection with this virus. Specimens drawn too early in the acute phase (e.g., before 8 to 10 days post-infection) may be negative for IgM-specific antibodies to WNV. If WNV is suspected, a second specimen drawn approximately 14 days postinfection should be tested. In the very early stages of WNV infection, IgM may be detectable in cerebrospinal fluid (CSF) before it becomes detectable in serum.

**Reference Values:** Only orderable as part of a profile. For more information see WNS / West Nile Virus Antibody, IgG and IgM, Serum.

Clinical Information: West Nile virus (WNV) is a mosquito-borne flavivirus (single-stranded RNA) that primarily infects birds but can also infect humans and horses. WNV was first isolated in 1937 from an infected person in the West Nile district of Uganda. Until the viral infection was recognized in 1999 in birds in New York City, WNV was found only in the Eastern Hemisphere, with wide distribution in Africa, Asia, the Middle East, and Europe. (1-3) Most recently, in 2012, a total of 5,674 cases of WNV were reported to the CDC, among which 2,873 (51%) were classified as neuroinvasive disease (e.g., meningoencephalitis) and 286 (5%) cases resulted in death. (2) Most people who are infected with WNV will not develop clinical signs of illness. It is estimated that about 20% of those who become infected will develop West Nile fever with mild symptoms, including fever, headache, myalgia, and occasionally a skin rash on the trunk of the body. Case fatality rates among patients hospitalized during recent outbreaks have ranged from 4% to 14%. Advanced age is the most important risk factor for death, and patients older than 70 years of age are at particularly high risk. (1) Laboratory diagnosis is best achieved by demonstration of specific IgG and IgM class antibodies in serum specimens. PCR (LCWNV / West Nile Virus, Molecular Detection, PCR) can detect WNV RNA in specimens from patients with recent WNV infection (i.e., 3-5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in cerebrospinal fluid and approximately 10% in blood, from patients with known WNV infection.

Useful For: Only orderable as part of a profile. See WNC / West Nile Virus Antibody, IgG and IgM, Spinal Fluid. Aid in diagnosis of central nervous system infection with West Nile virus

Interpretation: A positive result is consistent with the acute phase of West Nile virus (WNV) meningitis or encephalitis. In the very early stages of acute WNV infection, IgM may be detectable in cerebrospinal fluid before it becomes detectable in serum. A negative result may indicate absence of disease. However, specimens drawn too early in the acute phase may be negative for IgM-class antibodies to WNV. If WNV central nervous system infection is suspected, a second specimen should be collected in 1 to 2 weeks and tested.

Reference Values:
Only orderable as part of a profile. See WNC / West Nile Virus Antibody, IgG and IgM, Spinal Fluid.

IgM-class antibodies in serum specimens. PCR testing can detect WNV RNA in plasma specimens from patients with recent WNV infection (ie, 3-5 days following infection) when specific antibodies to the virus are not yet present. However, the likelihood of detection is relatively low as the sensitivity of PCR detection is approximately 55% in cerebrospinal fluid and approximately 10% in blood from patients with known WNV infection.

Useful For: Rapid testing for West Nile virus (WNV) RNA An adjunctive test to serology for detection of early WNV infection

Interpretation: A positive result indicates the presence of West Nile virus (WNV) RNA and is consistent with early WNV infection.

Reference Values:
Negative


Western Equine Encephalitis Antibody Panel, IgG and IgM, Spinal Fluid

Clinical Information: The virus that causes Western equine encephalitis (WEE) is widely distributed throughout the United States and Canada; disease occurs almost exclusively in the western states and Canadian provinces. The relative absence of the disease in the eastern United States probably reflects a paucity of the vector mosquito species, Culex tarsalis, and possibly a lower pathogenicity of local virus strains. The disease usually begins suddenly with malaise, fever, and headache, often with nausea and vomiting. Vertigo, photophobia, sore throat, respiratory symptoms, abdominal pain, and myalgia are also common. Over a few days, the headache intensifies; drowsiness and restlessness may merge into a coma in severe cases. In infants and children, the onset may be more abrupt than for adults. WEE should be suspected in any case of febrile central nervous system (CNS) disease from an endemic area. Infants are highly susceptible to CNS disease and about 20% of cases are under 1 year of age. There is an excess of males with WEE clinical encephalitis, averaging about twice the number of infections detected in females. After recovery from the acute disease, patients may require from several months to 2 years to overcome the fatigue, headache, and irritability. Infants and children are at a higher risk of permanent brain damage after recovery than adults. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age, sex, and occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age. WEE tends to produce the most severe clinical infections in young persons.

Useful For: Aiding the diagnosis of Western equine encephalitis

Interpretation: Detection of organism-specific antibodies in the cerebrospinal fluid (CSF) may suggest central nervous system (CNS) infection. However, these results are unable to distinguish between intrathecal antibodies and serum antibodies introduced into the CSF at the time of lumbar puncture or from a breakdown in the blood-brain barrier. The results should be interpreted with other laboratory and clinical data prior to a diagnosis of CNS infection.

Reference Values:
IgG: <1:10
IgM: <1:10
Reference values apply to all ages.

Western Equine Encephalitis Antibody, IgG and IgM, Serum

**Clinical Information:** The virus that causes Western equine encephalitis (WEE) is widely distributed throughout the United States and Canada; disease occurs almost exclusively in the western states and Canadian provinces. The relative absence of the disease in the eastern United States probably reflects a paucity of the vector mosquito species, Culex tarsalis, and possibly a lower pathogenicity of local virus strains. The disease usually begins suddenly with malaise, fever, and headache, often with nausea and vomiting. Vertigo, photophobia, sore throat, respiratory symptoms, abdominal pain, and myalgia are also common. Over a few days, the headache intensifies; drowsiness and restlessness may merge into a coma in severe cases. In infants and children, the onset may be more abrupt than for adults. WEE should be suspected in any case of febrile central nervous system (CNS) disease from an endemic area. Infants are highly susceptible to CNS disease and about 20% of cases are under 1 year of age. There is an excess of males with WEE clinical encephalitis, averaging about twice the number of infections detected in females. After recovery from acute disease, patients may require from several months to 2 years to overcome the fatigue, headache, and irritability. Infants and children are at higher risk of permanent brain damage after recovery than adults. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age, sex, and occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age. WEE tends to produce the most severe clinical infections in young persons.

**Useful For:** Aiding the diagnosis of Western equine encephalitis

**Interpretation:** In patients infected with this virus, IgG antibody is generally detectable within 1 to 3 weeks of onset, peaking within 1 to 2 months, and declining slowly thereafter. IgM class antibody is also reliably detected within 1 to 3 weeks of onset, peaking and rapidly declining within 3 months. Single serum specimen IgG > or =1:10 indicates exposure to the virus. Results from a single serum specimen can differentiate early (acute) infection from past infection with immunity if IgM is positive (suggests acute infection). A 4-fold or greater rise in IgG antibody titer in acute and convalescent sera indicate recent infection. In the United States it is unusual for any patient to show positive reactions to more than 1 of the arboviral antigens, although Western equine encephalitis (WEE) and Eastern equine encephalitis (EEE) antigens will show a noticeable cross-reactivity. Infections with arboviruses can occur at any age. The age distribution depends on the degree of exposure to the particular transmitting arthropod relating to age and sex, as well as the occupational, vocational, and recreational habits of the individuals. Once humans have been infected, the severity of the host response may be influenced by age: WEE tends to produce the most severe clinical infections in young persons. Infection in males is primarily due to working conditions and sports activity taking place where the vector is present.

**Reference Values:**

- IgG: <1:10
- IgM: <1:10

Reference values apply to all ages.

**Clinical References:**

Western Ragweed, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt; or =100</td>
<td>Strongly positive Reference values apply to all ages.</td>
</tr>
</tbody>
</table>


Wheat IgG

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation* 2.0 Upper Limit of Quantitation**

| 200 |

**Reference Values:**

< 2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food-specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.
**Wheat IgG4**

**Interpretation:** mcg/mL of IgG4 Lower Limit of Quantitation 0.15 Upper Limit of Quantitation 30.0

**Reference Values:**

<0.15 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG4 tests has not been clearly established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food related complaints, and to evaluate food allergic patients prior to food challenges. The presence of food-specific IgG4 alone cannot be taken as evidence of food allergy and only indicated immunologic sensitization to the food allergen in question.

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**Wheat, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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**Clinical References:** Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and
**Whey IgG**

**Interpretation:** mcg/mL of IgG Lower Limit of Quantitation 2.0 Upper Limit of Quantitation 200

**Reference Values:**

<2 mcg/mL

The reference range listed on the report is the lower limit of quantitation for the assay. The clinical utility of food-specific IgG tests has not been established. These tests can be used in special clinical situations to select foods for evaluation by diet elimination and challenge in patients who have food-related complaints. It should be recognized that the presence of food specific IgG alone cannot be taken as evidence of food allergy and only indicates immunologic sensitization by the food allergen in question. This test should only be ordered by physicians who recognize the limitations of the test.

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**Whey, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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Reference values apply to all ages.

**White Ash, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

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<tr>
<td>1</td>
<td>0.35-0.69</td>
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</tr>
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<td>2</td>
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Reference values apply to all ages.


**White Bean, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergens that may be associated with allergic disease. The allergens chosen for
testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease, the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

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**White Faced Hornet Venom, IgE**

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**Clinical References:** Homburger HA: Chapter 53: Allergic diseases. In Clinical Diagnosis and
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**White Hickory, IgE**

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<td>5</td>
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<td>Very High Positive</td>
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<tr>
<td>6</td>
<td>&gt;100</td>
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Reference values apply to all ages.


Whitefish IgE

Interpretation: Class IgE (kU/L) Comment 0 <0.10 Negative 0/1 0.10 â€“ 0.34 Equivocal 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.4 Moderate Positive 3 3.5 â€“ 17.4 High Positive 4 17.5 â€“ 49.9 Very High Positive 5 50.0 â€“ 99.9 Very High Positive 6 >100 Very High Positive

Reference Values: <0.35 kU/L

Whole Exome Sequencing

Clinical Information: Many patients with suspected genetic disorders remain without a diagnosis despite having a phenotype that is suggestive of an underlying genetic etiology, such as developmental delay and dysmorphic features. These diagnostic odyssey patients have often had numerous negative or
inconclusive genetic tests previously, including karyotype, chromosomal microarray, and various single or multigene assays. Identification of a specific diagnosis can assist in understanding the natural history of a condition, targeting medical management, and providing information to family members about the inheritance pattern and recurrence risks of the condition. This test uses next-generation sequencing technology to assess for variants within the coding regions (exons) of approximately 23,000 genes simultaneously. The patient's biological parents must be available and able to provide a blood sample, which is used for comparison purposes. Based upon published reports, a diagnosis is identified in trio-based whole exome sequencing in approximately 25% to 37% of cases.\(^{(2-4)}\) Indications for whole exome sequencing include but are not limited to:\(^{(5)}\) - Patient with a phenotype and/or family history that strongly suggests an underlying genetic cause, yet genetic tests for that phenotype have failed to arrive at a diagnosis (diagnostic odyssey patient) - Patient with a phenotype and/or family history that strongly suggests an underlying genetic cause, but the phenotype does not fit with one specific disorder (numerous individual genetic tests would be required for evaluation) - Patient with a suspected genetic disorder that has numerous underlying genetic causes, making analysis of numerous genes simultaneously a more practical approach than single-gene testing (condition is genetically heterogeneous) - Patient with a suspected genetic disorder for which specific molecular genetic testing is not yet available

See Whole Exome Sequencing (WES): Questions and Answers for Providers in Special Instructions for additional information.

**Useful For:** Identifying a molecular diagnosis in patients with a known or suspected genetic disorder, which can allow for: - Better understanding of the natural history/prognosis - Targeted management (anticipatory guidance, management changes, specific therapies) - Predictive testing of at-risk family members - Testing and exclusion of disease in siblings or other relatives - Recurrence risk assessment - Reproductive decision-making Serving as a second-tier test for patients in whom previous genetic testing for specific syndromes was negative Providing a potentially cost-effective alternative to establishing a molecular diagnosis compared to multiple independent molecular assays

**Interpretation:** All detected variants are evaluated according to American College of Medical Genetics and Genomics (ACMG) recommendations.\(^{(6)}\) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments and/or additional data detailing their potential or known significance. Patients who consent to receive medically actionable secondary findings are evaluated for pathogenic and likely pathogenic variants as recommended by ACMG.\(^{(1)}\) Variants of uncertain significance (VUS) in these genes are not reported. Parental origin of reportable variants is stated. Variants that are present in a parent but absent from the proband are not evaluated. The absence of a reportable secondary finding does not guarantee that there are no pathogenic or likely pathogenic variants in these genes, as portions of the genes may not be adequately covered by this testing methodology. If a patient opts-out of receiving these results, these variants will not be reported unless they occur in a gene that is clinically related to the patient's presenting phenotype.

**Reference Values:**
An interpretive report will be provided that includes variants likely causative of the patientâ€™s reported clinical features, variants possibly relevant to the patientâ€™s reported clinical features, variants in genes of uncertain significance (GUS), and medically actionable secondary findings (unless the patient opts out).

Wild Rye Grass, IgE

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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Wild Silk, IgE

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of WS.

**Useful For:** Establishing a diagnosis of Williams syndrome Detecting cryptic rearrangements involving 7q11.23 that are not demonstrated by conventional chromosome studies

**Interpretation:** The use of high-resolution chromosome studies and FISH for Williams syndrome chromosome region should diagnose about 96% of Williams syndrome patients and, at the same time, identify any other chromosome anomalies.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

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**Willow, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

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**WT1I**

**Wilms Tumor (WT-1) Immunostain, Technical Component Only**

**Clinical Information:** Wilms tumor-1 (WT-1) protein is a transcription factor that acts as a tumor suppressor gene. WT-1 is involved in differentiation of certain tissues such as mesothelium and the urogenital system. It is also expressed in Wilms tumor, a kidney tumor found in children. In normal tissues, it is expressed in kidney, a subset of hematopoietic cells, Sertoli cells in the testis, granulosa cells in the ovary, and decidual cells of the uterus.

**Useful For:** Aids in the identification of Wilms tumor

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to test code PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request. Contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.


**WDZ**

**Wilson Disease, Full Gene Analysis**

**Clinical Information:** Wilson disease (WD) is an autosomal recessive disorder that results from the body's inability to excrete excess copper. Typically, the liver releases excess copper into the bile. Individuals with WD lack the necessary enzyme that facilitates clearance of copper from the liver to bile. As a result, copper accumulates first in the liver and gradually in other organs. The brain, kidneys, bones, and corneas can also be affected. WD affects approximately 1 in 30,000 people worldwide, with a carrier frequency of approximately 1 in 90 individuals. The primary clinical manifestations of WD are hepatic and neurologic. Hepatic disease can be quite variable, ranging from hepatomegaly or other nonspecific symptoms that mimic viral hepatitis to severe liver damage, such as cirrhosis. Neurologic symptoms of WD can include poor fine-motor coordination, ataxia, and dysphagia. Psychiatric manifestations are reported in approximately 20% of individuals with WD. A characteristic ophthalmologic finding is the Kayser-Fleischer ring. Individuals with WD typically begin to show symptoms of liver dysfunction or neurologic disease in the first or second decade of life. If not treated, WD can cause liver failure, severe brain damage, and even death. A variety of laboratory tests are recommended in the initial evaluation for WD. In approximately 95% of cases, serum ceruloplasmin is below normal. Additionally, patients with WD show decreased copper in serum, increased copper in urine, and significantly elevated copper on liver biopsy. While liver biopsy is not recommended as a first-tier screening test for WD, it can be useful to help interpret discrepant biochemical or molecular results. The other tests should be performed prior to sequence analysis of the ATP7B gene, the gene responsible for WD. More than 300 disease-causing mutations have been identified in the ATP7B gene. Most mutations are family-specific with the exception of the H1069Q mutation, which accounts for...
>50% of identified disease alleles in the Northern European Caucasian population. See Wilson Disease Testing Algorithm in Special Instructions for additional information.

**Useful For:** Diagnostic confirmation of Wilson disease

**Interpretation:** All detected alterations are evaluated according to American College of Medical Genetics recommendations. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

**Reference Values:**
An interpretive report will be provided.

**Clinical References:**

**FWING**
57955

**Wingscale (Atriplex Canescens) IgE**

**Interpretation:**
Class IgE (kU/L) Comment
0 <0.35 Below Detection
1 0.35 – 0.69 Low Positive
2 0.70 – 3.49 Moderate Positive
3 3.50 – 17.49 Positive
4 17.50 – 49.99 Strong Positive
5 50.00 – 99.99 Very Strong Positive
6 >99.99 Very Strong Positive

**Reference Values:**
<0.35 kU/L

**WORM**
82680

**Wormwood, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**
Class IgE kU/L Interpretation
0 Negative
BUCCF

X and Y Aneuploidy Detection, Buccal Smear, FISH

Clinical Information: Aneuploidy of the sex chromosomes is common among recognized congenital syndromes. For example, the majority (80%) of individuals with Klinefelter syndrome have 2 X chromosomes and 1 Y chromosome; the remainder are mosaics or variants. Individuals with Turner syndrome have a single X chromosome in 55% of cases; the remaining 45% are either variants or mosaics. Conventional cytogenetic analysis should be performed for confirmation, especially when the results are abnormal. Structural abnormalities of X and Y chromosomes will be missed by this technique, as will low-level mosaicism. This test can detect between 50% to 70% of Turner syndrome cases (only those caused by complete lack of 1 sex chromosome [45,X] or high-level mosaicism for a 45,X). Congenital blood chromosome analysis (CMS / Chromosome Analysis, for Congenital Disorders, Blood) should always be performed for Turner syndrome. The test does not rule out numeric or structural cytogenetic anomalies involving chromosomes other than X and Y.

Useful For: Diagnosis of mosaic sex chromosome aneuploidy as a supplement to conventional chromosome studies in patients with normal or uncertain chromosome results or when an alternative tissue needs to be studied.

Interpretation: Specimens that contain >5% cells with a signal pattern other than XX in females and XY in males have a very high likelihood of having a clone of cells with an abnormal complement of sex chromosomes. Specimens with <5% of cells with a signal pattern other than XX in females and XY in males most likely do not have a clone of cells with an abnormal complement of sex chromosomes, but the presence of an abnormal clone of cells is not completely ruled out.

Reference Values: An interpretive report will be provided.


XALDZ

X-Linked Adrenoleukodystrophy, Full Gene Analysis

Clinical Information: X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disease characterized by magnetic resonance imaging (MRI) findings in the white matter, adrenocortical insufficiency, and abnormal plasma concentrations of very long chain fatty acids. The phenotypic expression of X-ALD varies widely. The phenotypes can be subdivided into 3 main categories: childhood cerebral form, adrenomyeloneuropathy (AMN), and Addison disease only. The childhood cerebral form has onset of symptoms between ages 4 and 8, beginning with attention deficit hyperactivity disorder-like symptoms with progressive cognitive, behavior, vision, hearing, and motor deterioration. AMN usually presents in males in their late twenties as progressive paraparesis, sexual dysfunction, sphincter disturbances, and abnormalities in adrenocortical function. The Addison only
phenotype typically presents by age 7.5 with adrenocortical insufficiency without significant neurological involvement. Most of these patients eventually develop AMN. Some female carriers may experience mild AMN symptoms with a later age of onset. The phenotype cannot be predicted by very long chain fatty acids (VLCFA) plasma concentration or by the nature of the mutation. The same mutation can be associated with each of the known phenotypes. Different phenotypes often occur within a family. POX / Fatty Acid Profile, Peroxisomal (C22-C26). Serum testing is the preferred first-tier screening method for X-ALD. This is abnormal in 99% of affected males and 85% of carrier females. Sequencing of the ABCD1 gene is available to confirm the diagnosis of X-ALD, improve carrier detection, and assist with prenatal diagnosis.

Useful For: Confirming a diagnosis of X-linked adrenoleukodystrophy Identifying a mutation in the ABCD1 gene

Interpretation: All detected alterations are evaluated according to American College of Medical Genetics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Reference Values:
An interpretive report will be provided.

Clinical References:

XHIM 82964

X-Linked Hyper IgM Syndrome, Blood

Clinical Information: CD154 (CD40 ligand: CD40L) is required for the interaction of T cells and B cells as part of the normal adaptive immune response. Activation of T cells leads to the expression of the CD40L molecule on the cell surface. CD40L binds the CD40 receptor that is always present on B cells, monocytes, and macrophages (regardless of environmental conditions). This interaction of CD40L with CD40 is important in B-cell proliferation, differentiation, and class-switch recombination (isotype class-switching). Patients with X-linked hyper-IgM (XL-HIGM) syndrome have defective CD40L expression on their activated helper CD4 T cells.(1,2) This leads to defective B-cell responses and the absence of immunoglobulin class-switching. These features are typified in these patients by a profound reduction or absence of isotype class-switched memory B cells (CD19+CD27+IgM-IgD-) with low or absent secreted IgG and IgA, and normal or elevated serum IgM levels.(1,2) Due to the impairment of T-cell function and macrophage activation, XL-HIGM patients are particularly prone to opportunistic infections with Pneumocystis jiroveci, Cryptosporidium, and Toxoplasma gondii.(1) To date, more than 100 unique mutations of CD40LG, the gene that encodes CD40L, have been described, affecting the intracellular, transmembrane and, more commonly, extracellular domain containing the CD40-binding region. A defect in surface expression of CD40L on activated CD4 T cells can be demonstrated using an anti-CD40L antibody and flow cytometry.(3,4) Since certain CD40LG mutations can maintain surface protein expression, albeit with loss of function, it is important to also evaluate CD40L-binding capacity to eliminate the possibility of false-negative results. A soluble recombinant, chimeric receptor protein, CD40-ulg, is incorporated into the assay, which assesses CD40L function by determining receptor-binding activity. Approximately 20% of XL-HIGM patients have activated CD4 T cells with normal surface expression of CD40L, but aberrant function.(4) XL-HIGM is a severe type of primary immunodeficiency that affects males, and most patients are diagnosed within a few months to the first year of life. Females are typically carriers and asymptomatic. Consequently, this test is only indicated in young males (<10 years of age) or, to identify carriers, in females of child-bearing age (<45 years).

Useful For: Screening for X-linked hyper-IgM (XL-HIGM) or CD40L deficiency, primarily in male patients younger than 10 years of age Ascertaining XL-HIGM carrier status in females of child-bearing age
age younger than 45 years of age

**Interpretation:** This is a qualitative assay; CD40L-protein expression and function is reported as present or absent. Absence of CD40L-protein expression and function is consistent with X-linked hyper-IgM (XL-HIGM). In females, the presence of 2 populations—normal and abnormal—is consistent with carrier status. Most patients (80%-90%) with XL-HIGM have absent or significantly reduced CD40L expression on their activated CD4 T cells. Patients with normal CD40L expression, but abnormal function, show an absence of binding with soluble chimeric CD40-ul1 antibody, substantiating a diagnosis of XL-HIGM. Females who are carriers for this disease will show a typical bimodal pattern of CD40L expression, with 50% of the T cells lacking any CD40L expression. In the case of aberrant protein function, a similar profile will be obtained with the CD40-ul1 antibody. CD69 is a marker for T-cell activation and serves as a positive control; in the absence of induced CD69 expression on T cells, the presence of XL-HIGM cannot be assessed.

**Reference Values:**

Present

**Clinical References:**


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**BMTF 35259**

**XX/XY in Opposite Sex Bone Marrow Transplantation, FISH**

**Clinical Information:** Bone marrow transplantation (BMT) continues to be an important treatment for patients with malignant hematologic disorders and bone marrow failure syndromes. Conventional cytogenetic studies can be performed to evaluate a mixture of donor and recipient cells in opposite sex bone marrow transplants at a sensitivity of approximately 5%. Interphase FISH testing for X and Y chromosomes in opposite sex bone marrow transplant specimens results in an improved sensitivity of approximately 0.5%.

**Useful For:** Evaluating engraftment success by determining the proportion of donor and recipient interphase cells present in opposite sex bone marrow transplant recipients Monitoring the proportion of host and recipient cells over time may be useful to identify significant clinical changes

**Interpretation:** Residual XX host cells are present in female BMT recipients when the percent of XX interphase cells exceeds the cutoff (>0.6% XX). Residual XY host cells are present in male BMT recipients when the percent of XY interphase cells exceeds the cutoff (>0.3% XY).

**Reference Values:**

An interpretive report will be provided.

**Clinical References:** Dewald GW, Schad CR, Christensen ER, et al: Fluorescence in situ hybridization with X and Y chromosome probes for cytogenetic studies on bone marrow cells after opposite sex transplantation. Bone Marrow Transplant 1993;12:149-154

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**YMCRO 35576**

**Y Chromosome Microdeletions, Molecular Detection**

**Clinical Information:** Yq microdeletions involving some or all of the azoospermic factor (AZF) region are the most frequently identified cause of spermatogenic failure in chromosomally normal men with nonobstructive azoospermia (3%-15%) or severe oligospermia (6%-10%). Among unselected infertile males, the overall frequency of Yq microdeletions is approximately 3%. The relative frequency of Yq microdeletions makes the evaluation for them an important aspect of the diagnostic work up in infertile males, especially those with azoospermia or severe oligospermia. Most cases of Yq microdeletions occur de novo, and due to the consequent infertile phenotype, they are typically not
transmitted. However, in cases where assisted reproductive technology (example: testicular sperm extraction followed by intracytoplasmic sperm injection) is used to achieve viable pregnancy, all male offspring born to a microdeletion carrier will carry the deletion and may be infertile. Men testing positive for 1 or more microdeletions who are enrolled in an in vitro fertilization treatment program may wish to consider alternative options to intracytoplasmic sperm injection (eg, donor sperm) and consultation with an experienced reproductive endocrinologist and medical geneticist is recommended. Most Y microdeletions are the result of homologous recombination between repeated sequence blocks. Testing for deletions involves investigating for the presence or absence of markers located within nonpolymorphic regions of the AZF region.

**Useful For:** Evaluating men with azoospermia, severe oligozoospermia, or otherwise unexplained male factor infertility

**Interpretation:** An interpretive report will be provided.

**Clinical References:**

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**Yellow Faced Hornet Venom, IgE**

**Clinical Information:** Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

**Useful For:** Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

**Interpretation:** Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE kU/L</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>1</td>
<td>0.35-0.69</td>
<td>Equivocal</td>
</tr>
<tr>
<td>2</td>
<td>0.70-3.49</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50-17.4</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.5-49.9</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>5</td>
<td>50.0-99.9</td>
<td>Strongly positive</td>
</tr>
</tbody>
</table>

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**Current as of October 11, 2018 2:20 pm CDT   800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com**
Clinical Information: Clinical manifestations of immediate hypersensitivity (allergic) diseases are caused by the release of proinflammatory mediators (histamine, leukotrienes, and prostaglandins) from immunoglobulin E (IgE)-sensitized effector cells (mast cells and basophils) when cell-bound IgE antibodies interact with allergen. In vitro serum testing for IgE antibodies provides an indication of the immune response to allergen(s) that may be associated with allergic disease. The allergens chosen for testing often depend upon the age of the patient, history of allergen exposure, season of the year, and clinical manifestations. In individuals predisposed to develop allergic disease(s), the sequence of sensitization and clinical manifestations proceed as follows: eczema and respiratory disease (rhinitis and bronchospasm) in infants and children less than 5 years due to food sensitivity (milk, egg, soy, and wheat proteins) followed by respiratory disease (rhinitis and asthma) in older children and adults due to sensitivity to inhalant allergens (dust mite, mold, and pollen inhalants).

Useful For: Testing for IgE antibodies may be useful to establish the diagnosis of an allergic disease and to define the allergens responsible for eliciting signs and symptoms. Testing also may be useful to identify allergens which may be responsible for allergic disease and/or anaphylactic episode, to confirm sensitization to particular allergens prior to beginning immunotherapy, and to investigate the specificity of allergic reactions to insect venom allergens, drugs, or chemical allergens.

Interpretation: Detection of IgE antibodies in serum (Class 1 or greater) indicates an increased likelihood of allergic disease as opposed to other etiologies and defines the allergens that may be responsible for eliciting signs and symptoms. The level of IgE antibodies in serum varies directly with the concentration of IgE antibodies expressed as a class score or kU/L.

Reference Values:
Class IgE kU/L Interpretation
0 Negative
1 0.35-0.69 Equivocal
2 0.70-3.49 Positive
3 3.50-17.4 Positive
4 17.5-49.9 Strongly positive
5 50.0-99.9 Strongly positive
6 > or =100 Strongly positive Reference values apply to all ages.
signaling pathway that is upregulated in sonic hedgehog-associated medulloblastomas and medulloblastomas with activation of the Wnt signaling pathway and is expressed on lung, placenta, prostate, ovary, and testis.

**Useful For:** Identification and differentiation of medulloblastomas

**Interpretation:** This test includes only technical performance of the stain (no pathologist interpretation is performed). Mayo Clinic cannot provide an interpretation of tech only stains outside the context of a pathology consultation. If an interpretation is needed, refer to PATHC / Pathology Consultation for a full diagnostic evaluation or second opinion of the case. All material associated with the case is required. Additional specific stains may be requested as part of the pathology consultation, and will be performed as necessary at the discretion of the Mayo pathologist. The positive and negative controls are verified as showing appropriate immunoreactivity and documentation is retained at Mayo Clinic Rochester. If a control tissue is not included on the slide, a scanned image of the relevant quality control tissue is available upon request; contact 855-516-8404. Interpretation of this test should be performed in the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

**Clinical References:**

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**FYABS**

**Yo Antibody Screen with Reflex to Titer and Western Blot**

**Reference Values:**

<table>
<thead>
<tr>
<th>Class</th>
<th>IgE (kU/L)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;0.35</td>
<td>Below Detection</td>
</tr>
<tr>
<td>1</td>
<td>0.35 - 0.69</td>
<td>Low Positive</td>
</tr>
<tr>
<td>2</td>
<td>0.70 - 3.49</td>
<td>Moderate Positive</td>
</tr>
<tr>
<td>3</td>
<td>3.50 - 17.50</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>17.50 - 49.99</td>
<td>Strong Positive</td>
</tr>
<tr>
<td>5</td>
<td>50.00 - 99.99</td>
<td>Very Strong Positive</td>
</tr>
<tr>
<td>6</td>
<td>&gt;99.99</td>
<td>Very Strong Positive</td>
</tr>
</tbody>
</table>

**FYOG**

**Yogurt (Lactobacillus bulgaricus) IgE**

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:**

<0.35 kU/L

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**MZIKV**

**Zika Virus IgM Antibody Capture MAC-ELISA, Serum**

**Clinical Information:** Zika virus is a RNA virus in the genus Flavivirus and is primarily transmitted through the bite of an infected Aedes species mosquito. Other means of transmission include through transfusion of blood and blood products, sexually through genital secretions, perinatally, vertically from mother to fetus, and potentially through contact with other body secretions such as tears and sweat. Historically, most cases of Zika virus infection have occurred in parts of Africa and South-East Asia. However, Zika virus emerged in South America in early 2015 and is now endemic in over 50 countries in South, Central, and North America, including in several US territories and focal regions of the southern United States. The majority (approximately 80%) of individuals infected with Zika virus are asymptomatic. Among symptomatic patients, fever, headache, retro-orbital pain, conjunctivitis, maculopapular rash, myalgias, and arthralgias are commonly reported. Notably, these symptoms are not distinct and can be seen with other emerging arboviruses, including dengue and chikungunya. Therefore,
diagnostic testing for each of these viruses is recommended in patients returning for areas where these viruses cocirculate. Intrauterine or prenatal infection with Zika virus has been causally linked to development of microcephaly, with the greatest risk for fetal abnormality occurring if the infection is acquired during the first trimester. Finally, Zika virus has also been associated with development of Guillain-Barre syndrome. A number of Zika virus serologic and nucleic acid amplification tests (NAAT) have received emergency use authorization (EUA) through the Food and Drug Administration (FDA). The recommended tests vary by the patient’s symptoms, course of illness, and whether or not the patient is pregnant. For the most up-to-date information regarding CDC testing guidelines visit www.cdc.gov/zika/.

These guidelines are reflected in the following testing algorithms in Special Instructions:

- Assessment for Zika Virus Infection in Nonpregnant Individuals
- Assessment for Zika Virus Infection in Pregnant Women

Zika virus testing is not recommended for asymptomatic couples attempting conception, given the potential for false-positive and false-negative results. Additionally, it is well established the Zika virus may remain in reproductive fluids, despite negative serologic and molecular test results in blood and urine.

**Useful For:** Screening for the presence of IgM-class antibodies to Zika virus in patients presenting with symptoms for 14 or more days. Establishment of baseline serologic levels of IgM-class antibodies to Zika virus in women who have traveled to a Zika virus endemic region or who have had sexual exposure to Zika virus and who are considering conception.

**Interpretation:** See the Zika virus algorithms in Special Instructions for a review of the recommended testing and interpretation of results. For the most recent CDC guidelines for Zika virus testing visit www.cdc.gov/zika/. Presumptive Zika Positive: IgM-class antibodies to Zika virus (ZIKV) detected. This is a preliminary result and does not confirm evidence of ZIKV infection. Definitive healthcare decisions should not be made based on this result alone. False-positive results may occur in patients with other current or prior flavivirus infections (eg, dengue virus). This specimen has been referred for confirmatory plaque reduction neutralization testing (PRNT) to the CDC or a CDC-designated laboratory.

For patients with less than 14 days of symptoms or last possible exposure to ZIKV, real-time (RT)-PCR for ZIKV on serum and urine is recommended. A positive ZIKV RT-PCR result on either specimen is confirmatory for ZIKV infection. Other Flavivirus Positive: Antibodies to a flavivirus, not Zika virus, were detected. Consider targeted testing for IgM-class antibodies to dengue and/or West Nile viruses as appropriate, taking into consideration patient exposure and presentation.

Negative: No evidence of IgM-class antibodies to Zika virus (ZIKV). For specimens collected less than 14 days postsymptom onset or possible ZIKV exposure, the CDC recommends RT-PCR for ZIKV on serum and urine to exclude a false-negative ZIKV IgM result.

**Reference Values:**

**Clinical References:**


**Zika Virus, PCR, Molecular Detection, Random, Urine**

**Clinical Information:** Zika virus is an RNA virus in the genus Flavivirus and is primarily transmitted through the bite of an infected Aedes species mosquito. Other means of transmission include through transfusion of blood and blood products, sexually through genital secretions, perinatally, vertically from mother to fetus, and potentially through contact with other body secretions such as tears and sweat. Historically, most cases of Zika virus infection have occurred in parts of Africa and South-East Asia. However, Zika virus emerged in South America in early 2015 and is now endemic in over 50 countries in South, Central, and North America, including in several US territories and focal regions of the southern United States. The majority (approximately 80%) of individuals infected with Zika virus are asymptomatic. Among symptomatic patients, fever, headache, retro-ocular pain,
conjunctivitis, maculopapular rash, myalgias and arthralgias are commonly reported. Notably, these symptoms are not distinct and can be seen with other emerging arboviruses, including dengue and chikungunya. Therefore, diagnostic testing for each of these viruses is recommended in patients returning for areas where these viruses cocirculate. Intrauterine or prenatal infection with Zika virus has been causally linked to development of microcephaly, with the greatest risk for fetal abnormality occurring if the infection is acquired during the first trimester. Finally, Zika virus has also been associated with development of Guillain-Barre syndrome. A number of Zika virus serologic and nucleic acid amplification tests (NAAT) have received emergency use authorization (EUA) through the Food and Drug Administration (FDA). The recommended tests vary by the patient's symptoms, course of illness, and whether or not the patient is pregnant. For the most up-to-date information regarding CDC testing guidelines visit www.cdc.gov/zika/. These guidelines are reflected in the following MML testing algorithms in Special Instructions:

Assessment for Zika Virus Infection in Nonpregnant Individuals
Assessment for Zika Virus Infection in Pregnant Women
Zika virus testing is not recommended for asymptomatic couples attempting conception, given the potential for false-positive and false-negative results. Additionally, it is well established the Zika virus may remain in reproductive fluids, despite negative serologic and molecular test results in blood and urine.

Useful For: Qualitative detection of Zika virus RNA in paired urine and serum from individuals meeting CDC Zika virus clinical or epidemiologic criteria

Interpretation: A positive test result indicates the presence of Zika virus RNA in the specimen. The FDA requires that urine specimens be tested in conjunction with a paired serum specimen. However, a positive result in either specimen is consistent with recent infection. A negative test result with a positive internal control indicates that Zika virus RNA is not detectable in the specimen. A negative test result with a negative internal control is considered evidence of PCR inhibition or reagent failure. A new specimen should be collected for testing if clinically indicated.

Reference Values:
Negative

Clinical References:

RZIKS 65181

Zika Virus, PCR, Molecular Detection, Serum

Clinical Information: Zika virus is an RNA virus in the genus Flavivirus and is primarily transmitted through the bite of an infected Aedes species mosquito. Other means of transmission include through transfusion of blood and blood products, sexually through genital secretions, perinatally, vertically from mother to fetus, and potentially through contact with other body secretions such as tears and sweat. Historically, most cases of Zika virus infection have occurred in parts of Africa and South-East Asia. However, Zika virus emerged in South America in early 2015 and is now endemic in over 50 countries in South, Central, and North America, including in several US territories and focal regions of the southern United States. The majority (approximately 80%) of individuals infected with Zika virus are asymptomatic. Among symptomatic patients, fever, headache, retro-orbital pain, conjunctivitis, maculopapular rash, myalgias and arthralgias are commonly reported. Notably, these symptoms are not distinct and can be seen with other emerging arboviruses, including dengue and chikungunya. Therefore, diagnostic testing for each of these viruses is recommended in patients returning for areas where these viruses cocirculate. Intrauterine or prenatal infection with Zika virus has been causally linked to development of microcephaly, with the greatest risk for fetal abnormality occurring if the infection is acquired during the first trimester. Finally, Zika virus has also been associated with development of Guillain-Barre syndrome. A number of Zika virus serologic and nucleic acid amplification tests (NAAT) have received emergency use authorization (EUA) through the Food and Drug Administration (FDA). The recommended tests vary by the patient's symptoms, course of illness, and whether or not the patient is pregnant. For the most up-to-date information regarding CDC testing guidelines visit www.cdc.gov/zika/.
These guidelines are reflected in the following MML testing algorithms in Special Instructions:

Assessment for Zika Virus Infection in Nonpregnant Individuals - Assessment for Zika Virus Infection in Pregnant Women

Zika virus testing is not recommended for asymptomatic couples attempting conception, given the potential for false-positive and false-negative results. Additionally, it is well established the Zika virus may remain in reproductive fluids, despite negative serologic and molecular test results in blood and urine.

**Useful For:** Qualitative detection of Zika virus RNA in serum from individuals meeting CDC Zika virus clinical or epidemiologic criteria

**Interpretation:** A positive test result indicates the presence of Zika virus RNA in the specimen. A negative test result with a positive internal control indicates that Zika virus RNA is not detectable in the specimen. A negative test result with a negative internal control is considered evidence of PCR inhibition or reagent failure. A new specimen should be collected for testing if clinically indicated.

**Reference Values:**

Negative

**Clinical References:**

2. United States Food and Drug Administration. Emergency Use Authorizations (Medical Devices). Available at www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm

**Zinc Protoporphyrin, Blood**

**Clinical Information:** The porphyrins are intermediaries in the heme synthesis pathway. When iron is not available for heme synthesis (eg, iron deficiency), zinc protoporphyrin (ZPP) accumulates within RBCs. Lead inhibits several enzymes in the heme synthesis pathway and causes increased levels of RBC ZPP. ZPP is a biological marker of lead toxicity and was previously used, in conjunction with blood lead assays, to screen for lead poisoning in children. However, because of poor sensitivity and specificity, ZPP is no longer recommended for lead screening in children. However, ZPP remains a useful tool for monitoring treatment of individuals with confirmed elevated lead levels.

**Useful For:** Evaluating iron deficiency Monitoring treatment and environmental intervention of chronic lead poisoning

**Interpretation:** An elevated zinc protoporphyrin (ZPP) indicates impairment of the heme biosynthetic pathway. Elevated ZPP levels in adults may indicate long-term (chronic) lead exposure or may be indicative of iron deficiency anemia or anemia of chronic disease.

**Reference Values:**

<70 mcmol ZPP/mol heme

**Clinical References:**


**Zinc Transporter 8 (ZnT8) Antibody, Serum**

**Useful For:**

**Interpretation:**

**Reference Values:**

<70 mcmol ZPP/mol heme
Clinical Information: Islet cell autoantibodies have been known to be associated with type 1 diabetes mellitus since the 1970s. Since 1988, several autoantigens against which islet antibodies are directed have been identified. These include the insulinoma-associated protein 2 (IA-2), glutamic acid decarboxylase 65 (GAD65), insulin, and, most recently, the zinc transporter ZnT8. Only 4% to 7% of patients with type 1 diabetes are autoantibody negative, fewer than 10% have only 1 marker, and around 70% have 3 or 4 markers. These findings have been confirmed in multiple specialty laboratories internationally. One or more of these autoantibodies are detected in 93% to 96% of patients with type 1 diabetes, both adults and children. These antibodies are also detectable in relatives of type 1 diabetic patients at risk for developing diabetes, before clinical onset. Because of symptom-onset in adulthood, societal obesity, and initial insulin-independence, some patients with type 1 diabetes are initially diagnosed as having type 2 diabetes. These patients with either "latent autoimmune diabetes in adulthood" or type 1 diabetes mellitus, may be distinguished from those patients with type 2 diabetes by detection of 1 or more islet autoantibodies, including ZnT8 antibody. Patients with gestational diabetes can also be stratified for future diabetes risk by detection of 1 or more islet autoantibodies (including ZnT8 antibody).

Useful For: Clinical distinction of type 1 from type 2 diabetes mellitus Identification of individuals at risk of type 1 diabetes (including high-risk relatives of patients with diabetes, and those with gestational diabetes) Prediction of future need for insulin treatment in adult-onset diabetic patients

Interpretation: Seropositivity for ZnT8 autoantibody (> or =15 IU/mL) is supportive of: -A diagnosis of type 1 diabetes -A high risk for future development of diabetes -A current or future need for insulin therapy in patients with diabetes

Reference Values: <15.0 U/mL


Zinc, 24 Hour, Urine

Clinical Information: Zinc is an essential element; it is a critical cofactor for carbonic anhydrase, alkaline phosphatase, RNA and DNA polymerases, alcohol dehydrogenase, and many other physiologically important proteins. Zinc also is a key element required for active wound healing. Zinc depletion occurs either because it is not absorbed from the diet or it is lost after absorption. Dietary deficiency may be due to absence (parenteral nutrition) or because the zinc in the diet is bound to fiber and not available for absorption. Once absorbed, the most common route of loss is via exudates from open wounds such as third-degree burns or gastrointestinal loss as in colitis. Hepatic cirrhosis also causes excess loss of zinc by enhancing renal excretion. The peptidase, kinase, and phosphorylase enzymes are most sensitive to zinc depletion. Zinc excess is not of major clinical concern. The popular American habit of taking mega-vitamins (containing huge doses of zinc) produces no direct toxicity problems. Much of this zinc passes through the gastrointestinal tract and is excreted in the feces. The excess fraction that is absorbed is excreted in the urine. The only known effect of excessive zinc ingestion relates to the fact that zinc interferes with copper absorption, which can lead to hypocupremia.

Useful For: Identifying the cause of abnormal serum zinc concentrations using a 24-hour urine specimen

Interpretation: Fecal excretion of zinc is the dominant route of elimination. Renal excretion is a
minor, secondary elimination pathway. Normal daily excretion of zinc in the urine is in the range of 20 to 967 mcg/24 hour. High urine zinc associated with low serum zinc may be caused by hepatic cirrhosis, neoplastic disease, or increased catabolism. High urine zinc with normal or elevated serum zinc indicates a large dietary source, usually in the form of high-dose vitamins. Low urine zinc with low serum zinc may be caused by dietary deficiency or loss through exudation common in burn patients and those with gastrointestinal losses.

Reference Values:
0-17 years: not established
> or =18 years: < or =967 mcg/24 hours


FZRBC 91949

Zinc, Red Blood Cell
Reference Values:
Zinc, Plasma: 70 - 120 ug/dL
Zinc, RBC: 1,000 - 1,600 ug/dL

ZNS 8620

 Zinc, Serum
Clinical Information: Zinc is an essential element; it is a critical cofactor for carbonic anhydrase, alkaline phosphatase, RNA and DNA polymerases, alcohol dehydrogenase, and many other physiologically important proteins. The peptidases, kinases, and phosphorylases are most sensitive to zinc depletion. Zinc is a key element required for active wound healing. Zinc depletion occurs either because it is not absorbed from the diet (excess copper or iron interfere with absorption) or it is lost after absorption. Dietary deficiency may be due to absence (parenteral nutrition) or because the zinc in the diet is bound to phytate (fiber) and not available for absorption. Excess copper and iron in the diet (eg, iron supplements) interfere with zinc uptake. Once absorbed, the most common route of loss is via exudates from open wounds or gastrointestinal loss. Zinc depletion occurs in burn patients who lose zinc in the exudates from their burn sites. Hepatic cirrhosis causes excess loss of zinc by enhancing renal excretion. Other diseases that cause low serum zinc are ulcerative colitis, Crohn's disease, regional enteritis, sprue, intestinal bypass, neoplastic disease, and increased catabolism induced by anabolic steroids. The conditions of anorexia and starvation also result in low zinc levels. Zinc excess is not of major clinical concern. The popular American habit of taking megavitamins (containing huge doses of zinc) produces no direct toxicity problems. Much of this zinc passes through the gastrointestinal tract and is excreted in the feces. The excess fraction that is absorbed is excreted in the urine. The only known effect of excessive zinc ingestion relates to the fact that zinc interferes with copper absorption, which can lead to hypocupremia.

Useful For: Detecting zinc deficiency

Interpretation: Normal serum zinc is 0.66 to 1.10 mcg/mL. Burn patients with acrodermatitis may have zinc as low as 0.4 mcg/mL; these patients respond quickly to zinc supplementation. Elevated serum zinc is of minimal clinical interest.

Reference Values:
0-10 years: 0.60-1.20 mcg/mL
> or =11 years: 0.66-1.10 mcg/mL

deficiency: cutaneous manifestations typical of acrodermatitis enteropathica. JAMA
zinc-supplemented and -unsupplemented healthy subjects during and after prolonged hypokinesia. Tr
Elem Electro 2008;25:60-68

**Zinc/Creatinine Ratio, Random, Urine**

**Clinical Information:** Zinc is an essential element; it is a critical cofactor for carbonic anhydrase,
alkaline phosphatase, RNA and DNA polymerases, alcohol dehydrogenase, and many other
physiologically important proteins. Zinc also is a key element required for active wound healing. Zinc
depletion occurs either because it is not absorbed from the diet or it is lost after absorption. Dietary
deficiency may be due to absence (parenteral nutrition) or because the zinc in the diet is bound to fiber
and not available for absorption. Once absorbed, the most common route of loss is via exudates from open
wounds such as third-degree burns or gastrointestinal loss as in colitis. Hepatic cirrhosis also causes
excess loss of zinc by enhancing renal excretion. The peptidase, kinase, and phosphorylase enzymes are
most sensitive to zinc depletion. Zinc excess is not of major clinical concern. The popular American habit
of taking mega-vitamins (containing huge doses of zinc) produces no direct toxicity problems. Much of
this zinc passes through the gastrointestinal tract and is excreted in the feces. The excess fraction that is
absorbed is excreted in the urine. The only known effect of excessive zinc ingestion relates to the fact that
zinc interferes with copper absorption, which can lead to hypocupremia.

**Useful For:** Identifying the cause of abnormal serum zinc concentrations using a random urine
specimen

**Interpretation:** Fecal excretion of zinc is the dominant route of elimination. Renal excretion is a
minor, secondary elimination pathway. Normal daily excretion of zinc in the urine is in the range of 89 to
910 mcg/g creatinine. High urine zinc associated with low serum zinc may be caused by hepatic cirrhosis,
neoplastic disease, or increased catabolism. High urine zinc with normal or elevated serum zinc indicates
a large dietary source, usually in the form of high-dose vitamins. Low urine zinc with low serum zinc may
be caused by dietary deficiency or loss through exudation common in burn patients and those with
gastrointestinal losses.

**Reference Values:**
0-17 years: not established
> or =18 years: 89-910 mcg/g Creatinine

**Clinical References:** 1. Sata F, Araki S, Murata K, et al: Behaviour of heavy metals in human urine
and blood following calcium disodium ethylenediamine tetraacetate injection: Observations in heavy
of cadmium, lead, nickel and zinc status in biological samples of smokers and nonsmokers hypertensive
Zinc utilization in zinc-supplemented and-unsupplemented healthy subjects during and after prolonged
hypokinesia. Tr Elem Electro 2008;25(2):60-68

**Ziprasidone (Geodone, Zeldox)**

**Reference Values:**
Units: ng/mL

Expected plasma concentrations in patients taking Recommended Daily Dosages: Up to 220 ng/mL

**Zolpidem (Ambien), serum or plasma**

**Reference Values:**
Units: ng/mL

Current as of October 11, 2018 2:20 pm CDT  800-533-1710 or 507-266-5700 or MayoMedicalLaboratories.com  Page 2382
Expected hypnotic zolpidem concentrations in patients taking recommended daily dosages: up to 250 ng/mL.

Toxic range has not been established.

**Zonisamide, Serum**

**Clinical Information:** Zonisamide (Zonegran) is approved as adjunctive therapy for partial seizures refractory to therapy with traditional anticonvulsants. Zonisamide is the pharmacologically active agent; metabolites are not active. Essentially 100% of the zonisamide dose is absorbed. Zonisamide binds to erythrocytes; approximately 88% of circulating zonisamide is bound in erythrocytes. Because the erythrocyte-bound zonisamide is inactive, and binding varies with blood concentration, the relationship between serum level and dose is not linear. Time to peak zonisamide concentration is 2 to 4 hours; time to peak is delayed by co-administration with food to 4 to 6 hours. Zonisamide is metabolized by N-acetyl transferase (NAT1), cytochrome P4503A4 (CyP3A4), and uridine diphosphate glucuronidation (UDPG). Zonisamide is eliminated in the urine predominantly as the parent drug (35%), N-acetyl zonisamide (15%), and as the glucuronide ester of reduced zonisamide (50%). Co-administration of drugs that affect NAT1, CyP3A4, and UDPG activity, such as phenytoin and carbamazepine, will decrease zonisamide concentration. A typical zonisamide dose administered to an adult is 400 to 600 mg/day, administered in 2 divided doses. The apparent volume of distribution of zonisamide is 1.5 L/kg. Approximately 40% of the zonisamide circulating in the serum is bound to proteins. Zonisamide protein binding is unaffected by other common anticonvulsant drugs. The elimination half-life from plasma is 50 to 60 hours; the elimination half-life from erythrocytes is >100 hours. Since zonisamide is cleared predominantly by the kidney, the daily dosage of zonisamide given to patients with creatinine clearance <20 mL/min should be reduced. Serum level monitoring is recommended for all patients to ensure appropriate dosing because: 1) patient response correlates with serum level, 2) serum level does not correlate with dose because of concentration-dependent erythrocyte binding, 3) elimination is affected by co-administration of drugs that affect NAT1, CyP3A4, and UDPG, and 4) renal function affects elimination. The most common toxicity associated with excessive serum level is drowsiness. Adverse effects not related to serum level include rash, increased serum creatinine and alkaline phosphatase, kidney stone formation, and bruising.

**Useful For:** Monitoring zonisamide therapy; recommended for all patients to ensure appropriate dosing Assessing medication compliance

**Interpretation:** Steady-state zonisamide concentration in a trough specimen drawn just before next dose correlates with patient response, but not with dose. Optimal response to zonisamide occurs when trough zonisamide concentration is in the range of 10 to 40 mcg/mL. Peak serum concentration for zonisamide occurs 2 to 6 hours after dose, and time to peak is affected by food intake. Because carbamazepine activates glucuronidation, patients taking carbamazepine concomitantly with zonisamide have significantly lower zonisamide concentrations compared to patients on the same dose not receiving carbamazepine.

**Reference Values:**
10-40 mcg/mL

**Clinical References:**
FZCCE
57562

Zucchini (Cucurbita spp) IgE

**Interpretation:** Class IgE (kU/L) Comment 0 <0.35 Below Detection 1 0.35 â€“ 0.69 Low Positive 2 0.70 â€“ 3.49 Moderate Positive 3 3.50 â€“ 17.49 Positive 4 17.50 â€“ 49.99 Strong Positive 5 50.00 â€“ 99.99 Very Strong Positive 6 >99.99 Very Strong Positive

**Reference Values:** <0.35 kU/L

MULT
35577

Zygosity Testing (Multiple Births)

**Clinical Information:** Approximately 30% of twins are monozygotic (identical), while 70% are dizygotic (nonidentical or fraternal). Monozygotic twins originate from a single egg, and by definition have identical DNA markers throughout their genomes. Dizygotic twins, on the other hand, inherit their genetic complement independently from each parent and are no more likely to have genetic material in common than are any other full siblings. To date, literally thousands of polymorphic DNA markers have been identified. DNA markers are regions of DNA that display normal variability in the type or the number of nucleotide bases at a given location. One particular class of repetitive DNA that exhibits marked variability is microsatellites. With the use of such markers, it is possible to distinguish one individual from another because of differences detected at these polymorphic loci. Utilizing PCR followed by gel electrophoresis, the genotypes of a set of twins (triplets, etc.) are derived from the analysis of multiple markers. This genotype is compared to those of their parents to determine if the children are mono- or dizygotic. Any differences detected between siblings' microsatellite markers indicate dizygosity. Many disorders are known to occur on a genetic basis though the genes have not been identified for all of them. If 1 member of a set of twins is diagnosed with a genetic disorder, determination of zygosity, in addition to other testing, may provide additional information regarding risk assessment of unaffected individuals. In addition, zygosity can be useful when evaluating for twin-twin transfusion syndrome during pregnancy or as part of a preorgan transplant workup for situations where one twin is donating an organ to another twin.

**Useful For:** Determining genetic risk for an individual whose twin or triplet is affected with a genetic disorder for which a specific genetic test is not available (or such testing is uninformative) Assessment of risks prenatally when 1 fetus of multiples is known to be affected by a specific disorder Organ or bone marrow transplantation compatibility testing Familial or parental interest

**Interpretation:** An interpretive report will be provided.

**Reference Values:** An interpretive report will be provided.